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Spontaneous ripples in the hippocampus correlate with epileptogenicity and not memory function in patients with refractory epilepsy

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ABSTRACT

Introduction: High-frequency oscillations (HFOs, 80–500 Hz) are newly-described EEG markers of epileptogenicity. The proportion of physiological and pathological HFOs is unclear, as frequency analysis is insufficient for separating the two types of events. For instance, ripples (80–250 Hz) also occur physiologically during memory consolidation processes in medial temporal lobe structures. We investigated the correlation between HFO rates and memory performance.

Methods: Patients investigated with bilateral medial temporal electrodes and an intellectual capacity allowing for memory testing were included. High-frequency oscillations were visually marked, and rates of HFOs were calculated for each channel during slow-wave sleep. Patients underwent three verbal and three nonverbal memory tests. They were grouped into severe impairment, some impairment, mostly intact, or intact for verbal and nonverbal memory. We calculated a Pearson correlation between HFO rates in the hippocampi and the memory category and compared HFO rates in each hippocampus with the corresponding (verbal — left, nonverbal — right) memory result using Wilcoxon rank-sum test.

Results: Twenty patients were included; ten had bilateral, five had unilateral, and five had no memory impairment. Unilateral memory impairment was verbal in one patient and nonverbal in four. There was no correlation between HFO rates and memory performance in seizure onset areas. There was, however, a significant negative correlation between the overall memory performance and ripple rates ($r = -0.50$, $p = 0.03$) outside the seizure onset zone.

Conclusion: Our results suggest that the majority of spontaneous hippocampal ripples, as defined in the present study, may reflect pathological activity, taking into account the association with memory impairment. The absence of negative correlation between memory performance and HFO rates in seizure onset areas could be explained by HFO rates in the SOZ being generally so high that differences between areas with remaining and impaired memory function cannot be seen.

1. Introduction

In patients with refractory epilepsy, a surgical removal of epileptic areas is the most promising treatment. Classical EEG markers to identify epileptogenic areas are interictal spikes and the seizure onset zone, which is defined as the area of the first ictal EEG changes. Intracranial EEG (iEEG) investigations are necessary if the epileptogenic focus cannot be identified with noninvasive methods such as MRI, surface EEG, and functional imaging or if results of these investigations are contradictory [1]. New markers for epileptogenic areas, which are recorded with iEEG, are high-frequency oscillations (HFOs) with frequencies between 80 and 500 Hz [2]. These oscillations are very small and short events (20–100 ms) and can be divided into ripple oscillations between 80 and 250 Hz and fast ripple oscillations between 250 and 500 Hz [3].

High-frequency oscillations were first described in recordings from microelectrodes in the medial temporal structures in humans and rodents [4,5]. In these recordings, fast ripples were found predominantly in epileptogenic areas, while ripples were most frequent in the medial temporal structures contralateral to the epilepsy focus [6,7]. As ripples had been described in the hippocampus in healthy animals and humans during processes of memory consolidation [8–10], it was hypothesized

Abbreviations: HFO, high-frequency oscillation; iEEG, intracranial EEG; MT, medial temporal; MTLE, medial temporal lobe epilepsy; SOZ, seizure onset zone; RAVLT, Rey Auditory Verbal Learning Test.

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that the ripples observed in humans might be physiological oscillations. The differentiation between physiological and pathological events in humans, however, is complicated as all recordings for ethical reasons are performed in patients with epilepsy and, thus, in more or less pathologically changed tissue [11].

The discussion of the origin of different types of HFOs was again raised when the first HFOs were recorded with macroelectrodes [12–14]. In contrast to the previous studies, these recordings showed an increase of both ripples and fast ripples in epileptogenic areas [15,16]. It was shown then that both ripples and fast ripples are increased in the SOZ [15–17]. In retrospective studies, the removal of tissue generating either type of oscillation is correlated with the postsurgical seizure outcome [18–20]. Thus, it seems likely that ripples, as well as fast ripples, might be indicators of epileptic tissue under certain circumstances, and the use of frequency analysis seems insufficient to differentiate between pathological and physiological oscillations [11]. Furthermore, it is uncertain whether the frequency separation between ripples and fast ripples is arbitrary or actually reflects two distinct types of oscillations [21]. The exact frequency distribution of HFOs may also depend on the electrodes used for analysis [14,22] or on brain regions sampled [23].

The identification of physiological HFOs in contrast to pathological HFOs is of great clinical importance, as a misinterpretation of physiological events as pathological could mislead physicians to removing brain areas that are functioning well and are not part of the epileptogenic network. Most studies on HFOs are performed in slow-wave sleep. While HFOs had only been related to tasks in neocortical areas [24,25], this is not the case in the medial temporal (MT) structures, where physiological HFOs are suggested to occur during sleep [24]. Thus, clinicians have to especially worry about the origin of oscillations when investigating temporal lobe epilepsy.

All surgical candidates undergo neuropsychological evaluations [26]. These aim to localize areas of dysfunction related to the epilepsy and also to identify brain regions important for the patient's functions. Memory function is often impaired in patients with epilepsy, and specific tests are available to test for verbal and nonverbal deficits [27,28]. In patients with left-dominant speech, verbal memory function is usually supported by the left hippocampus [29]. Its function can be tested with specific verbal memory tests such as the Rey Auditory Verbal Learning Test, the Story Learning and Memory test, or the Abstract Word List learning test [30,31]. The right hippocampus, in contrast, is more important for nonverbal memory processes, such as the memory of shapes, figures, and faces [28]. The Aggie Figures Learning Test, Abstract Design List learning test, Face Learning test, and the Rey–Osterrieth figure delayed recall test identify deficits in nonverbal memory function [28,32]. The detailed testing of memory function in presurgical patients provides an opportunity to evaluate the relationship between the occurrence of HFOs and memory function in the MT structures.

2. Methods

2.1. Patient selection and clinical evaluation

All patients who underwent intracranial EEG at the Montreal Neurological Institute with bitemporal implantations between September 2004 and March 2011 were considered for inclusion.

Patients had to fulfill the following criteria to be included in this study:

- Overall functioning and IQ which allowed a neuropsychological evaluation of memory function (IQ > 70);
- At least one electrode contact in the hippocampus on each side;
- Possibility to select an artifact-free interictal iEEG segment, with no seizure within 2 h prior to or after the selected segment.

Intracranial EEGs were performed exclusively for clinical reasons. This study was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee, and all patients signed an informed consent.

2.2. Recording methods and channel selection

Depth electrodes were implanted stereotactically using an image-guidance system (SSN Neuronavigation System, Mississauga, Ontario, Canada) according to the methods of Olivier et al. [33]. All electrodes were manufactured onsite, as described earlier [12,15]. Intracranial EEGs were recorded using Harmonie (Stellate, Montreal, Canada), low-pass filtered at 500 Hz and sampled at 2000 Hz. We recorded the electrooculogram (EOG) and electromyogram (EMG) to facilitate sleep staging. The recording was performed referentially with an epidural reference electrode placed in the parietal lobe of the hemisphere least likely to include the main focus. Analyses were performed on bipolar montages.

Either CT scans at the time of the intracranial investigation (available from 2009) or MRI scans after the removal of electrodes were used to evaluate which contacts of each electrode were located in the hippocampus. All contacts within the hippocampus and hippocampal–parahippocampal junction were selected for analysis. We analyzed interictal samples of slow-wave sleep lasting 5 to 10 min [21]. Periods of slow-wave sleep were selected using iEEG, EOG, and EMG, as described before [15].

2.3. Marking spikes and HFOs

The first minute of iEEG of each patient was marked by two reviewers (JJ and MZ) separately, and the concordance between marked events was assessed using Cohen's kappa coefficient for each channel. Both observers jointly reviewed the events in channels with kappa below 0.5 [34] and established a consensus on which events to retain. Based on this consensus, the remaining 4 min of iEEG were marked by one of the reviewers. A detailed description of the visual identification has been published [20]. In short, a ripple was marked if an event was clearly visible with an 80-Hz high-pass filter and did not occur when filtering with 250 Hz. An event was regarded as a fast ripple if it was visible in the 250-Hz filter. Rates of ripples, fast ripples, and spikes were calculated for each channel.

2.4. Clinical data

The seizure onset zone (SOZ) was defined by an experienced neurophysiologist independent of this study. In patients in whom seizures originated independently from both MT structures, both hippocampi were considered as the SOZ. Results of MRI, including volumetric studies of the hippocampus and other clinical information, were taken from each patient's hospital files.

2.5. Neuropsychological evaluation of memory

All patients underwent neuropsychological testing within six months of the intracranial implantation. They received a full presurgical investigation that included evaluation of frontal and temporal lobe functions and IQ testing, and *e*SAM studies [35] were also performed to determine hemispheric dominance for language.

For verbal memory, the patients underwent the following tests:

- Rey Auditory Verbal Learning Test (RAVLT),
- Story Learning and Memory test (SLaM),
- Abstract Word List learning test (AWL).

For nonverbal memory, the following tests were performed:

- Aggie Figures Learning Test (AFLT),
- Abstract Design List learning test (ADL),
- Face Learning and Recognition test.