Influence of contact size on the detection of HFOs in human intracerebral EEG recordings

C.E. Châtillon^{a,*}, R. Zemann^b, J.A. Hall^a, A. Olivier^a, F. Dubeau^c, and J. Gotman^b

^aDepartment of Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Canada

^bMontreal Neurological Institute, McGill University, Montreal, Canada

^cDepartment of Neurology, Montreal Neurological Institute, McGill University, Montreal, Canada

Abstract

Objective—High frequency oscillations (HFOs) are brief electroencephalographic events associated with epileptic activity, and likely representing biological markers of the epileptogenic zone. HFOs are usually detected with intracranial EEG and detection is influenced by contact size. The size of commercially available intracerebral electrodes varies widely. This study assesses HFO detection rates from adjacent electrode contacts in human intracerebral recordings.

Methods—Intracerebral recordings were collected from 11 patients undergoing stereoelectroencephalographic investigation using hybrid depth electrodes containing adjacent large (0.8 or 5 mm²) and small (0.2 or 0.3 mm²) contacts. HFOs were marked manually during 5-min tracings in 131 pairs of adjacent large and small contacts. HFO rates per minute and mean event durations were compared between adjacent contacts.

Results—A minimal but statistically significant advantage in ripple detection was found in a subgroup of large contacts. Otherwise, HFO rates and mean event durations were not statistically different between groups.

Conclusion—The size of clinical contacts within the studied range did not influence HFO detection in a clinically relevant manner. Larger contacts provide a minimal advantage for ripple detection.

Significance—Our findings suggest that commercially available intracerebral electrodes with contacts between 0.2 and 5 mm² likely possess similar HFO detection abilities.

Keywords

High frequency oscillations; Ripples; Intracerebral recordings; Stereoelectroencephalography

*Corresponding author. Address: Montreal Neurological Institute, 3801 University Street, Room 767, Montreal, Quebec, Canada H3A 2B4. Tel.: +1 514 398 1953; fax: +1 514 398 8106. claud-edouard.chatillon@mail.mcgill.ca (C.E. Châtillon).

Conflicts of interest: None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

1. Introduction

High frequency oscillations (HFOs) are brief, low-amplitude, high-frequency electroencephalographic (EEG) events associated with physiological neural processes, such as memory and sensory processing (Suzuki and Smith, 1988; Curio et al., 1994; Ylinen et al., 1995; Chrobak and Buzsaki, 1996; Barth, 2003; Ponomarenko et al., 2008), but also with pathological processes, in particular epilepsy (Bragin et al., 2000a, 2004; Staba et al., 2007; Jacobs et al., 2009a). HFOs have commonly been divided into two subtypes, based on frequency: ripples (80–250 Hz) and fast ripples (FRs, 250–500 Hz). Recent studies suggest that HFOs may be a useful clinical marker of the epileptogenic zone (Jacobs et al., 2010a; Akiyama et al., 2011; Modur et al., 2011). Indeed, these retrospective studies have shown post-operative patient outcome to correlate with the extent of resection of HFO-generating areas.

Initial studies of HFOs in rat epilepsy models and in epileptic patients were performed using microelectrodes ($<60\text{ }\mu\text{m}$ diameter, surface area (s.a.) $<0.001\text{ mm}^2$) (Buzsaki et al., 1992; Bragin et al., 1999b, 2000b, 2002b; Staba et al., 2002). Microwires, by virtue of their small size, sample the neuronal activity of a restricted brain volume surrounding the electrode. This may be advantageous for detection of HFOs, which are thought to be generated by very localized neuronal clusters (Bragin et al., 2000b, 2002a). However, this limited sampling volume does not allow for clinical EEG recordings; therefore clinical “macroelectrodes” must be used concomitantly in human intracranial investigations to provide classical SEEG tracings. Furthermore, microwires require specialized recording equipment due to their inherent high impedance.

HFOs can also be recorded using commercially available human intracerebral recording electrodes contacts with a s.a. of 2.5 to 20 mm² (Worrell et al., 2004; Akiyama et al., 2011, 2005; Gardner et al., 2007; Ochi et al., 2007; Otsubo et al., 2008; Worrell et al., 2008; Modur et al., 2011). At the Montreal Neurological Institute (MNI), proprietary intracerebral electrodes, having a 0.8 mm² contact s.a., have also demonstrated their ability to record HFOs (Jirsch et al., 2006; Urrestarazu et al., 2007; Jacobs et al., 2008). Larger contacts have a theoretical disadvantage for HFO detection because they record from a larger volume of brain tissue; therefore very localized low amplitude EEG events, such as HFOs, may be “drowned” in background electrical activity. If such events are visible on recordings from larger contacts, there is a potential advantage in sampling a larger volume of cerebral tissue in that a greater number of HFO-generating foci may be included in the recorded volume. Recently, Worrell and colleagues (2008) have shown that clinical contacts have a decreased ability to detect HFOs, especially in the higher frequency range (250–500 Hz) compared to adjacent microwires. Despite this drawback, clinical “macrocontacts” are increasingly being used for clinical HFO studies due to the convenience of using the same recordings for classical SEEG interpretation and HFO investigations. In this context, and considering that intracerebral recording electrodes consist of contacts of variable size, ranging from 2.5 to 20 mm² (Table 1), it is hypothesized that contact size, within the clinical range, may influence HFO detectability.

This study aims to evaluate the influence of contact size on HFO detection from adjacent contacts in human SEEG recordings using two types of hybrid intracerebral electrodes: MNI type, with adjacent 0.2 and 0.8 mm² contacts, and DIXI type, with adjacent 0.3 and 5 mm² contacts.

2. Methods

2.1. Patient selection

All patients undergoing SEEG investigation at the MNI as part of the pre-surgical evaluation of their intractable focal epilepsy between November 1st, 2007 and March 31st, 2009 were included in this study (Supplementary Table S1).

2.2. Intracerebral electrode types and contact sizes

At the MNI, two electrode types are routinely implanted for SEEG recordings. The first type is the previously mentioned in-house manufactured electrode ("MNI" in Table 1) composed of coated stainless steel wires of variable lengths, stripped at the tip and coiled at 5 mm intervals along a rigid stainless steel wire core. These wires constitute the 9 large contacts (s.a. = 0.8 mm²) of the MNI electrode. Two smaller contacts were added (s.a. = 0.2 mm²) located 1 mm proximal to the two deepest large contacts. The second type of electrode used at the MNI is the DIXI MicroDeep depth electrode (DixiMedical, France), which is composed of 10 – 14 cylindrical platinum-iridium contacts (s.a. = 5.0 mm²) at 3.5 mm intervals (center to center). Four to 8 smaller contacts (s.a. = 0.3 mm²) were added, each of which was interposed between two large contacts. Small contacts were paired with one adjacent large contact, in order to perform repeated samples statistical analyses.

2.3. SEEG segment selection and analysis

All patients underwent at least one overnight recording at 2000 Hz sampling rate with a 500 Hz high frequency hardware filter to avoid aliasing artefact, using the Harmonie system (Stellate, Montreal, Canada; amplifier input impedance = 50 MΩ). From this recording, a 5-min interictal segment of slow-wave sleep was selected for analysis. Channels were analyzed in referential montage. Channel order was shuffled and channel names were masked from the reviewer to avoid marking bias based on knowledge of a specific channel's size. All events were marked manually by a single reviewer (CEC). Spikes and sharp transients were marked on single channels at the following parameters: high-pass filter 0.3 Hz, sensitivity 30 μV/mm, 10 s/page, eight channels/page.

In this study, ripples were defined as brief events, clearly different from baseline and composed of at least four complete oscillations in the 80–250 Hz range. EEG was visualized with a high-pass filter at 80 Hz, 1.5 μV/mm, 0.8 s/page, eight channels/page. FRs were defined as brief events, clearly different from baseline and composed of at least four complete oscillations in the 250–500 Hz range. EEG was visualized with a high-pass filter at 250 Hz, 1.5 μV/mm, 0.8 s/page, eight channels/page.

Event characteristics for each channel were compiled using a Matlab algorithm. Analyses of HFO rates and duration as a function of contact size were performed by running repeated

samples non-parametric statistical tests (Wilcoxon's tests) using SPSS (IBM). Non-parametric statistics were selected because of the heavily right-skewed distribution of the data (not shown). Large/small contact pairs were excluded from the rates comparisons if both values were zero; contact pairs were excluded from duration comparisons if at least one of the two values was zero. Analysis of HFO duration as a function of electrode type was performed on pooled mean duration values per channel, using independent samples non-parametric tests (Kruskal-Wallis test, Mann-Whitney *U* test for post-hoc analyses). *P*-value significance was set at 0.05.

The research protocol for this study was reviewed and approved by the MNI ethics committee.

3. Results

Five minute SEEG recordings were obtained from 10 patients implanted with MNI electrodes and three patients implanted with DIXI electrodes. Two patients from the MNI electrode population were excluded prior to marking because of significant 250 Hz artefact which hindered visual marking of HFOs in more than 30% of the channels. In the remaining eight, 43 contact pairs (one "small" and one "large" contact) could be analysed: they were located in the amygdala (eight pairs), the hippocampal head (eight pairs), the posterior hippocampus (seven pairs) and mesial or basal neocortical structures (20 pairs). In the three DIXI patients, all 88 implanted contact pairs were kept for analysis. They were located in the amygdala (seven pairs), the hippocampal head (seven pairs), the posterior hippocampus (five pairs) and mesial or basal neocortical structures (69 pairs).

In the MNI population, 8137 spikes, 19793 ripples and 2132 FRs were recorded in 86 contacts, whereas 9533 spikes, 11372 ripples and 1438 FRs were recorded in 176 contacts from the DIXI population. The co-occurrence patterns of HFOs with spikes were very similar between large and small contacts (Fig. 1). Although the co-occurrence patterns were different between the MNI and DIXI populations, the overall proportions were maintained: most ripples occurred in isolation, most FRs occurred in association with ripples or spikes. In the MNI population, 61,0% of spikes contained HFOs, compared to 64,4% in the DIXI population.

Statistical analysis revealed a significant advantage in ripple rate detection using large contact sizes in the MNI electrode population (median (Mdn) = 10.8 vs 8.9 ripples/min; $Z = -3.019$, $p = 0.003$; Fig. 2A). However, the overall characteristics of the population for ripple rates (mean, median, extent and shape of the distribution) were very similar between large and small contact channels (Fig. 3). Statistical comparison of all other HFO rates and durations in the MNI and DIXI electrode populations did not yield any significant differences between large and small contact groups (Figs. 2 and 4).

Overall event durations were also compared as a function of electrode type. FR durations were statistically similar between the two groups (MNI Mdn = 24.4 ms, DIXI Mdn = 26.2 ms). Ripple durations were significantly longer in the DIXI population (MNI Mdn = 65.6 ms, DIXI Mdn = 81.4 ms; $p = 0.001$).

4. Discussion

An increasing number of HFO clinical studies involve intracranial EEG recordings using clinical, commercially available “macro-contacts” (Worrell et al., 2004; Akiyama et al., 2005; Jirsch et al., 2006; Gardner et al., 2007; Ochi et al., 2007; Urrestarazu et al., 2007; Jacobs et al., 2008; Worrell et al., 2008; Jacobs et al., 2009a; Jacobs et al., 2009b; Zijlmans et al., 2009a; Zijlmans et al., 2009b; Jacobs et al., 2010a; Jacobs et al., 2010b; Akiyama et al., 2011; Kobayashi et al., 2011; Modur et al., 2011). Using these methods, several recent studies have suggested that HFOs are reliable markers of the seizure onset zone (Jacobs et al., 2010a; Akiyama et al., 2011; Modur et al., 2011). Therefore, clinical HFO recordings are likely to play an important role in pre-surgical epilepsy investigations in the future. In this context, the optimization of HFO detection methodology is an important step towards the clinical use of HFO data. In 2008, a study by Worrell et al. (Worrell et al., 2008) demonstrated the superiority of microwire recordings for HFO detection, especially in the higher frequency (FR) range. However, the small sampling area covered by microwires does not allow for concomitant “clinical” EEG recordings, therefore clinical electrodes must be inserted in addition to microwires. This becomes a disadvantage because of the need for hybrid electrodes (containing “micro” and “macro” contacts), additional connexion equipment (wires, connectors, pre-amplifiers) and supplementary data storage. But the study by Worrell and colleagues (Worrell et al., 2008) raises the question whether contact size, even within the range of commercially available intracerebral electrodes, may influence HFO detection.

A recent study by our group (Châtillon et al., 2011) showed that contact size, within a range of 0.02 to 0.9 mm², did not affect HFO detection rates in a rat epilepsy model. The current study aimed to demonstrate whether these findings also applied to patients undergoing clinical SEEG recordings. Specifically, the usual “large” contacts from MNI and commercially available DIXI electrodes were compared to adjacent smaller contacts (respectively 4 and 16 times smaller than the adjacent large contact). The hypothesis, extrapolated from the Worrell and colleagues (2008) findings, was that smaller contact size conferred an advantage for HFO detection. Overall, our results demonstrate no statistically significant difference between contact sizes, with one exception: an increase in ripple rate detection was found for the large contacts in the MNI electrode population. As discussed earlier, a possible justification of this finding is the increased sampling volume of the large contacts, allowing them to record from a greater number of HFO foci. The lack of significant difference for FRs could be attributed to the overall low FR rates. However, this seems an unlikely explanation considering the lack of significant difference in HFO rates in the DIXI population, where the disparity in size between adjacent contacts is larger than in the MNI population. This incongruity may be attributed to the usually low signal amplitude of HFOs, whereby the increased recorded brain volume by large contacts is counterbalanced at some point by a better detection of individual events by small contacts. In any event, these differences are unlikely to have clinical relevance considering the minimal difference in mean rate and the almost complete distribution overlap between the compared groups; see Fig. 4). Overall, these findings suggest that HFOs can be detected similarly by electrodes with a surface area ranging from 0.2 to 5 mm².

In a second instance, event durations were analysed as an index HFO characteristic between the different groups, as an indicator that the compared events are of similar nature. However, it can also be hypothesized that HFO duration will vary as a function of a recording contact's sensitivity: HFOs usually do not appear and disappear abruptly, their amplitude increases to reach a maximum, then decreases over a variable period. Small differences in HFO detectability may therefore manifest themselves by a variable ability to record the "tails" of the event before any changes in detection rates are seen. In this study, ripple and FR mean durations per channel were not statistically different between adjacent large and small contacts, reinforcing the final findings from the analysis of HFO rates.

HFO durations were also compared between the two electrode type populations (MNI and DIXI). It must be stressed that, whereas the previous comparisons were performed on adjacent contacts on a single electrode from one patient, the following comparison is based on pooled results from two groups of patients with variations in epilepsy type and electrode localization. FR durations were found to be similar between the MNI and DIXI populations. However, ripple durations were significantly longer in the DIXI population (Mdn = 81.4 ms) compared to the MNI population (Mdn = 65.6 ms) ($p = 0.001$; Table 2). The most likely explanation for this difference seems to be sampling bias. Of the three patients in the DIXI population, two had median ripple rates similar to those of the MNI electrodes and to rates reported in previous studies (patient 8, Mdn = 72.8 ms; patient 11, Mdn = 60.1 ms), whereas patient 7 had a median ripple rate of 93.6 ms, shifting the population duration values upwards. This value, although significantly higher, falls within the range of MNI ripple durations and within previously published ripple duration ranges (Table 2). Furthermore, a similarly high median ripple duration was also found in one patient of the MNI population (patient 6, Mdn = 90.8 ms). These two patients with higher ripple durations did not share other distinctive features (etiology, location of electrodes, HFO rates) to explain this finding. Contact size is an unlikely cause of this finding because the compared size ranges of the two populations were overlapping (MNI: 0.2 vs 1 mm²; DIXI: 0.3 vs 5 mm²), and durations were similar between contact sizes. Nonetheless, intrinsic physical properties of the contacts can play a role in signal detection by changing the impedance. Indeed, the ratio of contact impedance (I_C) to input impedance (I_I) can produce signal attenuation as it increases, however this effect is usually considered insignificant if this ratio is very small (typically less than 1%). MNI contacts were manufactured using a 0.076 mm diameter stainless steel wire; impedances measured at 500 Hz were 6–8 k Ω for the large and 9–10 k Ω for the small contacts. DIXI electrodes consisted of 90% platinum, 10% iridium alloy contact plate connected to a 0.06 mm diameter Pt-Ir wire; impedances at 500 Hz were 430–480 Ω for the large and 4.4–4.8 k Ω for the small contacts. These values indicate that impedances of the MNI contacts, large and small, were higher than impedances of the small DIXI contacts. Considering a constant amplifier input impedance (50 M Ω), the I_C/I_I ratio of electrode contacts in this study are all inferior to 0.02%; differences should therefore be insignificant. This argument is reinforced by the fact that FR rates and durations were not statistically different between the two populations, when lower amplitude, higher frequency events (FRs) should be more susceptible to signal attenuation than their greater amplitude, lower frequency ripple counterparts.

4.1. Comparison with previous studies

The mean HFO rates reported in this study compare favorably with previous studies where HFO rates per channel are reported. Indeed, Bragin and colleagues (Bragin et al., 1999a,b) reported mean rates of 5.0 ripples/min and 2.1 FRs/min using microwire intracranial recordings in epileptic patients (Table 2). In comparison, mean FR rates observed in our study are similar (MNI = 2.5 FRs/min and DIXI = 1.7 FRs/min), whereas ripple rates are greater (MNI = 23.0 ripples/min and DIXI = 13.4 ripples/min), suggesting that macrocontacts may improve ripple detection compared to microwires. However, this difference may also be due to distinct HFO detection methods between the two studies: Bragin et al. performed an initial screening using power spectral analysis to focus their visual analysis on distinct high-frequency peaks, while in our study the raw data were all scanned visually. A second confounding factor may be the difference in patient populations between the two studies: Bragin and colleagues investigated exclusively mesial temporal contacts in patients with mesial temporal lobe epilepsy, whereas in this study, only 6 of 11 patients were suspected of temporal lobe epilepsy and a majority of channels (178/262) were located outside mesial temporal structures (Supplementary Table S1). This second factor is probably of lesser importance because HFO rates tend to be higher in mesial temporal structures (Jacobs et al., 2008), a trend also found in this study (data not shown).

4.2. Limitations

The main limitation of this study is the relatively narrow contact size range (0.2–5 mm²) we used for comparison (commercially available intracerebral electrode contact sizes range from 2.5 to 20 mm²). Nonetheless, we have shown that HFO detectability is not improved by the use of smaller contacts in this range, and in fact, large contacts were equivalent or marginally superior to detect HFOs compared to adjacent small contacts (MNI electrode population's ripple rates). Considering recent findings that ripples can be recorded from scalp EEG (Kobayashi et al., 2010; Andrade-Valenca et al., 2011), the use of even larger contacts than those studied here may allow and perhaps improve ripple detection by increasing the sampling volume of the recording electrode. Further studies using combined scalp and intracranial electrodes should allow further confirmation of this finding.

The contact sizes used in this study were limited by feasibility and patient safety issues: the hybrid electrodes had to be produced using the same materials, overall design and manufacture method as the previously used clinical electrodes. This limitation affected not only the size of the contacts that could be added, but also the number of additional contacts in order to maintain the same overall electrode dimensions. This explains the small number and size of the added small contacts (two for MNI, four to eight for DIXI electrodes).

5. Conclusion

The size of clinical contacts within the studied range did not influence HFO detection in a clinically relevant manner. Our findings also suggest that different types of intracerebral recording electrodes with contacts up to 5 mm² in s.a. possess similar HFO detection abilities. Larger contacts may slightly improve detection of HFOs in the ripple range by increasing the cortical volume being sampled. To the authors' knowledge, this study is the

first to evaluate the influence of contact size, within the clinical range, on HFO detection in humans. As the number of HFO studies using a variety of intracranial electrodes increases, this study strengthens the reliability of clinical “macrocontacts” for HFO detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was funded by the Canadian Institute of Health Research (CIHR) grant MOP-10189, a Centers of Excellence in Commercialization and Research (CECR) grant and the Savoy Foundation for Epilepsy. The authors would like to acknowledge the contribution of the EEG lab staff of the MNI, in particular Lorraine Allard and Nicole Drouin, for their collaboration in obtaining the intracerebral EEG recordings and preparation of the recordings for analysis.

References

- Akiyama T, McCoy B, Go CY, Ochi A, Elliott IM, Akiyama M, et al. Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. *Epilepsia*. 2011; 52:1802–11. [PubMed: 21801168]
- Akiyama T, Otsubo H, Ochi A, Ishiguro T, Kadokura G, Ramachandranair R, et al. Focal cortical high-frequency oscillations trigger epileptic spasms: confirmation by digital video subdural EEG. *Clin Neurophysiol*. 2005; 116:2819–25. [PubMed: 16253550]
- Andrade-Valenca LP, Dubeau F, Mari F, Zemann R, Gotman J. Interictal scalp fast oscillations as a marker of the seizure onset zone. *Neurology*. 2011; 77:524–31. [PubMed: 21753167]
- Barth DS. Submillisecond synchronization of fast electrical oscillations in neocortex. *J Neurosci*. 2003; 23:2502–10. [PubMed: 12657711]
- Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsaki G. High-frequency oscillations in human brain. *Hippocampus*. 1999a; 9:137–42. [PubMed: 10226774]
- Bragin A, Engel J Jr, Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. *Epilepsia*. 1999b; 40:127–37. [PubMed: 9952257]
- Bragin A, Mody I, Wilson CL, Engel J Jr. Local generation of fast ripples in epileptic brain. *J Neurosci*. 2002a; 22:2012–21. [PubMed: 11880532]
- Bragin A, Wilson CL, Almajano J, Mody I, Engel J Jr. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. *Epilepsia*. 2004; 45:1017–23. [PubMed: 15329064]
- Bragin A, Wilson CL, Engel J Jr. Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. *Epilepsia*. 2000a; 41(Suppl 6):S144–52. [PubMed: 10999536]
- Bragin A, Wilson CL, Staba R, Fried I, Reddick M, Engel J. Ripples and fast ripples in the human epileptic brain. Depth profiles and unit correlates. *Epilepsia*. 2000b; 41:8. abstract 1.019 (AES proceedings). [PubMed: 11156513]
- Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J Jr. Interictal high-frequency oscillations (80–500 Hz) in the human epileptic brain: entorhinal cortex. *Ann Neurol*. 2002b; 52:407–15. [PubMed: 12325068]
- Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K. High-frequency network oscillation in the hippocampus. *Science*. 1992; 256:1025–7. [PubMed: 1589772]
- Châtillon C-É, Zemann R, Bortel A, Avoli M, Gotman J. Contact size does not affect high frequency oscillation detection in intracerebral EEG recordings in a rat epilepsy model. *Clin Neurophysiol*. 2011; 122:1701–5. [PubMed: 21429792]
- Chrobak JJ, Buzsaki G. High-frequency oscillations in the output networks of the hippocampal-entorhinal axis of the freely behaving rat. *J Neurosci*. 1996; 16:3056–66. [PubMed: 8622135]

- Curio G, Mackert BM, Burghoff M, Koetitz R, Abraham-Fuchs K, Harer W. Localization of evoked neuromagnetic 600 Hz activity in the cerebral somatosensory system. *Electroencephalogr Clin Neurophysiol*. 1994; 91:483–7. [PubMed: 7529687]
- Gardner AB, Worrell GA, Marsh E, Dlugos D, Litt B. Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings. *Clin Neurophysiol*. 2007; 118:1134–43. [PubMed: 17382583]
- Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia*. 2008; 49:1893–907. [PubMed: 18479382]
- Jacobs J, Levan P, Chatillon CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain*. 2009a; 132:1022–37. [PubMed: 19297507]
- Jacobs J, Zelmann R, Jirsch J, Chander R, Dubeau C-ÉCF, Gotman J. High frequency oscillations (80–500 Hz) in the preictal period in patients with focal seizures. *Epilepsia*. 2009b; 50:1780–92. [PubMed: 19400871]
- Jacobs J, Zijlmans M, Zelmann R, Chatillon CE, Hall J, Olivier A, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol*. 2010a; 67:209–20. [PubMed: 20225281]
- Jacobs J, Zijlmans M, Zelmann R, Olivier A, Hall J, Gotman J, et al. Value of electrical stimulation and high frequency oscillations (80–500 Hz) in identifying epileptogenic areas during intracranial EEG recordings. *Epilepsia*. 2010b; 51:573–82. [PubMed: 19845730]
- Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. *Brain*. 2006; 129:1593–608. [PubMed: 16632553]
- Kobayashi K, Watanabe Y, Inoue T, Oka M, Yoshinaga H, Ohtsuka Y. Scalp-recorded high-frequency oscillations in childhood sleep-induced electrical status epilepticus. *Epilepsia*. 2010; 51:2190–4. [PubMed: 20384717]
- Kobayashi K, Yoshinaga H, Toda Y, Inoue T, Oka M, Ohtsuka Y. High-frequency oscillations in idiopathic partial epilepsy of childhood. *Epilepsia*. 2011; 52:1812–9. [PubMed: 21762448]
- Modur PN, Zhang S, Vitaz TW. Ictal high-frequency oscillations in neocortical epilepsy: implications for seizure localization and surgical resection. *Epilepsia*. 2011; 52:1792–801. [PubMed: 21762451]
- Ochi A, Otsubo H, Donner EJ, Elliott I, Iwata R, Funaki T, et al. Dynamic changes of ictal high-frequency oscillations in neocortical epilepsy: using multiple band frequency analysis. *Epilepsia*. 2007; 48:286–96. [PubMed: 17295622]
- Otsubo H, Ochi A, Imai K, Akiyama T, Fujimoto A, Go C, et al. High-frequency oscillations of ictal muscle activity and epileptogenic discharges on intracranial EEG in a temporal lobe epilepsy patient. *Clin Neurophysiol*. 2008; 119:862–8. [PubMed: 18289931]
- Ponomarenko AA, Li JS, Korotkova TM, Huston JP, Haas HL. Frequency of network synchronization in the hippocampus marks learning. *Eur J Neurosci*. 2008; 27:3035–42. [PubMed: 18588541]
- Staba RJ, Frigetto L, Behnke EJ, Mathern GW, Fields T, Bragin A, et al. Increased fast ripple to ripple ratios correlate with reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients. *Epilepsia*. 2007; 48:2130–8. [PubMed: 17662059]
- Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr. Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *J Neurophysiol*. 2002; 88:1743–52. [PubMed: 12364503]
- Suzuki SS, Smith GK. Spontaneous EEG spikes in the normal hippocampus. II. Relations to synchronous burst discharges. *Electroencephalogr Clin Neurophysiol*. 1988; 69:532–40. [PubMed: 2453330]
- Urrestarazu E, Chander R, Dubeau F, Gotman J. Interictal high-frequency oscillations (100–500 Hz) in the intracerebral EEG of epileptic patients. *Brain*. 2007; 130:2354–66. [PubMed: 17626037]
- Worrell GA, Gardner AB, Stead SM, Hu S, Goerss S, Cascino GJ, et al. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain*. 2008; 131:928–37. [PubMed: 18263625]

- Worrell GA, Parish L, Cranstoun SD, Jonas R, Baltuch G, Litt B. High-frequency oscillations and seizure generation in neocortical epilepsy. *Brain*. 2004; 127:1496–506. [PubMed: 15155522]
- Ylinen A, Bragin A, Nadasdy Z, Jando G, Szabo I, Sik A, et al. Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J Neurosci*. 1995; 15:30–46. [PubMed: 7823136]
- Zijlmans M, Jacobs J, Zelmann R, Dubeau F, Gotman J. High-frequency oscillations mirror disease activity in patients with epilepsy. *Neurology*. 2009a; 72:979–86. [PubMed: 19289737]
- Zijlmans M, Jacobs J, Zelmann R, Dubeau F, Gotman J. High frequency oscillations and seizure frequency in patients with focal epilepsy. *Epilepsy Res*. 2009b; 85:287–92. [PubMed: 19403269]

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.clinph.2013.02.113>.

HIGHLIGHTS

- High frequency oscillations (HFOs) can be detected by clinical intracranial electrodes of various sizes.
- Intracerebral electrodes ranging from 0.2 to 5.0 mm² possess similar HFO detection abilities.
- Larger contacts may provide an advantage for ripple detection.

Fig. 1. Distribution of HFOs and co-occurrence of individual events with other HFOs and spikes in patients implanted with MNI and DIXI electrodes. A majority of ripples occur in isolation, whereas most FRs occur concomitantly with ripples or spikes. Sp = spike, R = ripple, FR = fast ripple.

Fig. 2.

Box and whisker plot of rate versus contact size in the (A) MNI and (B) DIXI electrode populations. Values located 2 interquartile ranges away from the median are represented as outliers (-). * $p = 0.003$.

Fig. 3.
Frequency histogram of mean ripple rate per channel in the small and large contact groups of the MNI population.

Fig. 4. Box and whisker plot of mean event durations versus contact size in the (A) MNI and (B) DIXI electrode populations. Values located ± 2 interquartile ranges away from the median are represented as outliers (—).

Table 1

Different electrode types used for intracerebral recordings and their respective range in surface areas.

Manufacturer	Type	Material	Contact size (mm ²)	Intercontact distance (mm)
DIXI	Depth	Pt-Ir	5.0	3.5
Ad-Tech	Depth	Pt	3.14–9.4	5–10
PMT	Depth	Pt or SS	8.0–19.6	3–5
MNI	Depth	SS	0.8	5
DIXI	Subdural	Pt-Ir	4.9	10
Ad-Tech	Subdural	Pt or SS	2.5–4.2	10
PMT	Subdural	Pt or SS	3.1–15.9	10

Pt: platinum; Ir: iridium, SS: stainless steel.

Table 2

Comparison of HFO characteristics from previous reports using microelectrodes (Bragin et al., 1999a,b) and from the current study (using macroelectrodes). The current study values consist of pooled event characteristics from the large and small contact groups. Values from previous studies were reported as means and ranges.

		Châtillon et al. Median (range)		Bragin et al. Mean (range)
		MNI	DIXI	
Ripples	Rate (event/min)	10.4 (0–219.8)	6.5 (0–182.0)	5 (0.1–20)
	Duration (msec)	64.8 (43.8–143.0)	81.4 (36.0–144.3)	60 (50–120)
FRs	Rate (event/min)	1.2 (0–42.0)	1.0 (0–16.3)	2.1 (0.5–6)
	Duration (msec)	24.4 (15.0–76.0)	26.2 (14.5–70.5)	23 (10–40)