Progress Report 2014

Single-unit dynamics in the epileptic foci in patients with temporal lobe epilepsy

EPIDYN

PN-II-ID-PCE-2011-3-0240

Contract 153/2011

Single Units Activity in Patients with Epilepsy

Andrei Barborica, Ioana Mindruta, Jean Ciurea, Cristi Donos, Bogdan Balanescu

Single-unit activity

- Spontaneous Activity
 - Requires semi-chronic electrodes and long-term monitoring to capture at least one ictal event
 - Halgren et al. 1977; Wyler et al 1982; Babb et al 1987; Engel et al 2005; Keller et al, 2010
- Stimulation-induced Activity
 - Allows testing of neuronal responses in epileptogenic areas without having to wait for spontaneous events
 - Current EPIDYN study in our centers UB+SUUB+SCUBA: intraoperative mapping of single-unit responses to stimulation
 - Concurrent work: In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation – King's College, UK, 2012, Gonzalo Alarcón, Juan Martinez, Shashivadan V. Kerai, Maria E. Lacruz, Rodrigo Quian Quiroga, Richard P. Selway, Mark P. Richardson, Jorge J. García Seoane, Antonio Valentín Clinical Neurophysiology 123 (2012) 1736–1744

What do we know so far

Some neurons increase firing during seizures, some do the opposite



Single unit rasters for 131 neurons simultaneously recorded during an ictal episode. One has to note the heterogeneity of the firing in the initial phase of the seizure (most active neurons are shown on top, while least active at bottom), as well as the common feature of a nearly complete firing suppression towards the end of the seizure.

Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, Brown EN, Halgren E, Cash SS. Nat Neurosci. 2011 May;14(5):635-41.



Seizure 1 in Patient C had a relatively short duration (~ 11 s). Heterogeneous spiking behavior is most prominent during the first 5 seconds of the seizure. During the second half of the seizure, several synchronized bursts of activity can also be seen in the population spike rate and in the percentage of active neurons, synchronous with the repetitive discharges seen in EEG recordings. These bursts, interspaced with brief silences, resemble failed seizure terminations. After a postictal silence lasting ~ 5 s, a brief period of higher activity follows. Truccolo et al, Nature Neuroscience, 2011 (doi:10.1038/nn.2782)

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• Seizure 1 in Patient D appeared as a very mild event at the microelectrode site. It can be hardly detected on the population spike count rate, in the percentage of coactive neurons or in the Fano factor for the spike counts across the population. Nevertheless, visual inspection of the spike rasters reveals two main neuronal groups: one neuronal group with a buildup in activity (starting around 20 seconds into the seizure) and the other with a decrease during the initial 30-40 seconds. Based on ECoG analyses, the seizure lasted for 43 seconds.



Fig 3. Dot raster of a unit's activity in which the unit fired most commonly during the rising phase of the electrocorticographically recorded spike.

Fig 4. Example of a unit that fired predominantly during the falling phase of the electrocorticographic spike.

• Wyler, A.R., Ojemann, G.A. & Ward, A.A. Jr. Neurons in human epileptic cortex: correlation between unit and EEG activity. Ann. Neurol. 11, 301–308 (1982)

Phase locking?

• Well, not always!



Fig 1. Dot raster of unit activity centered around a spike recorded from the immediate overlying cortex (top line). Dots represent occurrence of action potentials (AP), whereas dashes represent sweeps in which no unit activity was recorded within the time window of this raster. At bottom is a histogram of AP occurrence with relationship to spike peak.



Fig 2. Raster of two units recorded simultaneously through the same microelectrode and their relationship to the electrocorticographic spike recorded from the microdrive presser foot. Dots represent action potentials (AP) from the large unit, whereas vertical bars represent APs from the small unit. At bottom is a histogram of AP occurrence from the large unit and the small unit.

fired predominantly in bursts (although not at particularly high frequency) immediately preceding the

Wyler, A.R., Ojemann, G.A. & Ward, A.A. Jr. Neurons in human epileptic cortex: correlation between unit and EEG activity. Ann. Neurol. 11, 301–308 (1982)



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Clinical Neurophysiology



journal homepage: www.elsevier.com/locate/clinph

In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation

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- The neuronal firing patterns during interictal epileptiform discharges (IEDs) and after single pulse electrical stimulation (SPES) can be described as burst-only, suppression-only, burst-suppression or no-change.
- Similar neuronal firing patterns can be observed during IEDs and after SPES.
- IEDs and responses to SPES appear to activate similar and generic cortical mechanisms, which may explain transient cognitive impairment.



Peri-IED vs peri-stim firing

- Modern times, G. Alarcón et al., 2012: Microwire recordings in amygdala, hippocampus or medial frontal cortex
- Stim on adjacent macro-contacts









Direct Activation of Sparse, Distributed Populations of Cortical Neurons by Electrical Microstimulation

What do we stimulate?

Mark H. Histed,1,* Vincent Bonin,1 and R. Clay Reid1,*



EPIDYN Study

- Intraoperative single-unit recording in SOZ
 - SOZ was assessed based on detailed SEEG investigations
 - previous studies were not necessarily recording in SOZ, as its location was not known at the time of the implantation
 - responses to repetitive stimulation of different frequencies and amplitudes
 - analyzing responses during stimulation by performing stimulus artifact suppression



Figure 1. Acute microelectrode recording setup using clinical electrodes, stereotactic positioning, stimulation and recording instrumentation commonly used for functional mapping in deep brain stimulation procedures

Subjects and Methods

We performed SEEG presurgical evaluation of 11 patients with drug-resistant focal epilepsy to locate the seizureonset zone (SOZ) and delineate the area to be resected.

Patient	Sex	Age	Pathology	Epilepsy	SOZ
1	F	32	Type I cortical dysplasia	Temporal	Mesial structures
2	М	46	Hippocampal sclerosis	Mesio-temporal	Amygdala
3	М	39	MCD temporo-occipital basal	Occipital	Basal
4	М	47	DNET	Temporal	Middle temporal gyrus
5	F	40	Type II B cortical dysplsia	Prefrontal	DLPFC
6	F	35	Gliosis	Mesio-temporal	Amygdala
7	F	25	Type II cortical dysplasia	Temporal	Temporal pole
8	F	46	Type II cortical dysplasia	Temporal	Temporal pole
9	М	33	Type I cortical dysplasia	Frontal	Anterior cingulate cortex
10	М	28	Type I cortical dysplasia	Temporal	Hippocampus
11	F	25	N/A	Temporal	Entorhinal cortex

Prior to the resective surgery, we are stereotactically inserting three microelectrodes, spaced 2mm apart, in a linear configuration, following a trajectory targeting SOZ. Standard clinical microelectrodes and equipment used in functional mapping for deep brain stimulation implantations was used. Bipolar electrical stimulation is applied in most cases between the two outer macro contacts of the electrodes, while recording the unit activity on the center microelectrode, located 3 mm deeper than the macro contacts. Constant current 0.5 to 1 mA biphasic pulses, 0.3 ms pulse width, frequency 1, 10, 30, 60 and 130 Hz were applied for 30 s using a clinical recording and stimulating system (Guideline LP+, FHC Inc, Bowdoin, ME). The interval before, between and after each electrical stimulation epoch was at least 30 seconds.

In order to remove the stimulation artifact, we used SALPA algorithm (Wagenaar and Potter, 2002). In addition, the noise introduced by connecting the stimulator to the macro contacts used for stimulation has been removed by using an adaptive noise cancellation filter (Widrow, 1975) using as reference the signal on one of the other microelectrode. This was possible as the stimulator noise on all channels is originating from a single source, therefore it is correlated across channels. Simultaneously sampled channels and built-in stimulation unit sharing the same clock as the recording unit resulted in a stimulation artifact without any pulse to pulse variability, therefore facilitating artifact removal (Hashimoto and Vitek, 2002). Spike sorting was performed using FIND toolbox (Meier et al., 2008).

Methodology: adaptive filtering of stimulus artifact and stimulator noise

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						Time (s)						



Figure 2. Illustration of the recording while stimulating, stimulus artifact removal and spike discrimination. a) the 1-Hz stimulation epoch recorded in patient 7 with discriminated neurons highlighted in red; b) a detail of the end of the stimulation epoch, showing the raw signal (gray) and the filtered signal. One has to note the noise band during stimulation that is significantly reduced. c) example of neurons recovered from the 30-Hz stimulation epoch. The blanking interval is 4.16 ms, accounting for 4.16% of the inter-pulse interval at 10 Hz and 25% at 60 Hz. d) mean spike waveform of the neuron presented in a), b) and c).

Adaptive Noise Cancelling: Principles and Applications

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Abstract-This paper describes the concept of adaptive noise cancelling, an alternative method of estimating signals corrupted by additive noise or interference. The method uses a "primary" input containing the corrupted signal and a "reference" input containing noise correlated in some unknown way with the primary noise. The reference input is adaptively filtered and subtracted from the primary input to obtain the signal estimate. Adaptive filtering before subtraction allows the treatment of inputs that are deterministic or stochastic, stationary or time variable. Wiener solutions are developed to describe asymptotic adaptive performance and output signal-to-noise ratio for stationary stochastic inputs, including single and multiple reference inputs. These solutions show that when the reference input is free of signal and certain other conditions are met noise in the primary input can be essentially eliminated without signal distortion. It is further shown that in treating periodic interference the adaptive noise canceller acts as a notch filter with narrow bandwidth, infinite null, and the capability of tracking the exact frequency of the interference; in this case the canceller behaves as a linear, time-invariant system, with the adaptive filter converging on a dynamic rather than a static solution. Experimental results are presented that illustrate the usefulness of the adaptive noise cancelling technique in a variety of practical applications. These applications include the cancelling of various forms of periodic interference in electrocardiography. the cancelling of periodic interference in

We cancel the stimulator noise (not the stimulation artifact) that is correlated across channels, as it originates from the same source.



Results

We have recorded to date 20 neurons in SOZ and adjacent areas. We were able to find several firing patterns in response to electrical stimulation: no-change (-0.25 < MI_{STIM} < 0.25), enhancement (MI_{STIM} > 0.25) or suppression (MI_{STIM} < -0.25), as shown in tables 2 and 3. The modulation is highly dependent on the stimulation frequency and pathology: 13 out of 14 neurons in SOZ exhibited suppression or enhancement at 30 Hz, compared to 4 out of 6 neurons outside SOZ. A buildup of the firing rate over the stimulation duration was observed in 12 (85.7%) of the SOZ neurons and 4 (66.6%) of the non-SOZ neurons at 30 Hz. Stimulation frequency above 30 Hz had a relative suppressive effect on the neuronal firing.



Figure 3. Illustration of a SOZ neuron highly modulated by the application of stimulation pulses, in patient #5 (prefrontal cortical dysplasia). The mean firing rate is little modified by the 1Hz stimulation (1.00 vs 1.70Hz), whereas at higher frequencies, it increases significantly to 2.57, 9.71 and 5.29 Hz for 10, 30 and 60 Hz, respectively. The higher firing rate is associated with increased time-locking of -0.25, 0.47, 0.93, 0.93 for the four stimulation frequencies.



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Correlation of single-unit firing pattern with EEG biomarkers of epileptogenicity during single-pulse electrical stimulation (SPES) in patient 10 (see Barborica et al 2013 for details) on SPES protocol). (a) Microelectrode trajectory shown on the MRI. The single unit was recorded from SOZ (Hc type I dysplasia). (b) Signal after artifact removal (c) Raster plot and firing rate histogram. (d) Peri-stimulus rasters and histograms for the inter-pulse interval. IPI histograms for 10 Hz and above exhibit a first peak around 10ms and a second one around 80 ms. (e) Unfiltered EEG response evoked by SPES in depth electrode's contact B03 (located in anterior Hippocampus, close to the microelectrode recording location) when stimulating on contact pair B05-B06 (located 3.5mm away). (f) Stimulus-response curve for pulses in the range 0.25 mA to 5 mA (3 ms, biphasic). (g) Time-frequency map of the responses, showing high-frequency oscillations (HFO) around 10 ms and 80 ms post-stimulation. (h,I,j) Similar to panel (e,f,g) but with the EEG signal filtered in the HFO frequency band (100-250Hz). The HFO at 10ms is now visible on both the EEG traces and the time-frequency map.

Patient 3 (LG)

• Microelectrode targeting SOZ - Amygdala



Patient 3 (LG)



Microtelectrode trajectory - probe eye view

SEEG + µE in Pat3 (LG)













μE Recordings in SOZ of Pat3 (LG)

Some neurons do not change firing during st

- Pat3-S1-4 d=-16.5mm, I=0.5mA, f=1Hz - 60 Hz







μE Recordings in SOZ of Pat3 (LG)

f=1, 10, 30, 60 Hz

- Moderate phasic response to stimulation pulses ~10ms
 - Pat3-S1-4 I=0.5mA,



Additional Examples



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Single Uni	t Statistics							
U								
Stim epoch enhancem	ent/suppression index							
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz			
All neurons	0.08±0.49, n=78	0.09±0.47, n=20	-0.03±0.39, n=20	0.20±0.55, n=20	0.07±0.55, n=18			
soz	0.08±0.51, n=55	0.06±0.46, n=14	-0.09±0.36, n=14	0.20±0.59, n=14	0.15±0.61, n=13			
non-SOZ	0.09±0.46, n=23	0.16±0.54, n=6	0.11±0.46, n=6	0.19±0.50, n=6	-0.14±0.33, n=5			
n-way anova analysis								
Factor	p							
Patient	0.0107	,						
Pathology	0.1058	8						
Frequency	0.4707	,						
Timelocking index								
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz			
All neurons	0.16±0.42, n=78	-0.09±0.25, n=20	0.26±0.53, n=20	0.27±0.46, n=20	0.20±0.29, n=18			
SOZ	0.22±0.48, n=55	-0.12±0.29, n=14	0.34±0.61, n=14	0.38±0.51, n=14	0.28±0.29, n=13			
non-SOZ	0.01±0.11, n=23	-0.02±0.11, n=6	0.05±0.05, n=6	0.03±0.13, n=6	-0.02±0.15, n=5			
n-way anova analysis								
Factor	p)						
Patient	0.0001							
Pathology	0.0168	8						
Frequency	0.0024							
Stim epoch buildup in	dex							
	All frequencies	1 Hz	10 Hz	30 Hz	60 Hz			
All neurons	-0.09±0.38, n=78	0.02±0.38, n=20	-0.07±0.29, n=20	-0.16±0.26, n=20	-0.18±0.54, n=18			
SOZ	-0.14±0.40, n=55	-0.03±0.33, n=14	-0.13±0.31, n=14	-0.16±0.28, n=14	-0.25±0.62, n=13			
non-SOZ	0.02±0.30, n=23	0.15±0.47, n=6	0.05±0.21, n=6	-0.15±0.22, n=6	0.01±0.18, n=5			
n-way anova analysis								
Factor	p							
Patient	0.2023							
Pathology	0.1038	8						
Frequency	0.3016	j						

Table 1. N-way ANOVA analysis on single units data. The results show that only the patient selection had a significant effect (p<0.05) on the stimulation epoch enhancement/suppression index. All three factors (patients selection, pathology and stimulation frequency) had significant effect (p<0.05) on the timelocking index. In the case of stimulation epoch buildup index, none of the three factors showed a significant effect (p<0.05).

Patholog Y	Stim Epoch Pattern	Inter-Pulse Pattern		Frequency (Hz)																		
			1					10				30					60					
			n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement (+) / Suppression(-)	Time- locking index	n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement (+) / Suppression(-)	Time- locking index	n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement(+) / Suppression(-)	Time- locking index	n	Baseline (Hz)	Stim Epoch (Hz)	Enhancement(+) / Suppression(-)	Time- locking index
soz	No-change	No-change	3	3 4.6	5 4.5	0.7%	1.2%	1	13.6	5 11.9	-6.5%	-5.6%	(C				C)			
		Time-locked	-	1 6.3	5.0	-12.0%	-17.2%	0					:	1 6.6	5 7.4	5.6%	62.2%	3	3 5.1	4.9	-2.8%	6 23.0%
	Enhancemen																	_				
	t	No-change		2 0.2	2 4.5	66.7%	-2.4%	1	2.1	. 2.9	15.8%	6 -41.7%		3 1.2	. 5.0	61.5%	5.0%	3	3 2.8	9.1	74.9%	<mark>6</mark> 39.9%
		Time-locked	3	3 9.6	5 13.4	42.9%	-16.8%	4	2.9	5.3	35.1%	65.5%		5 3.8	9.3	54.7%	65.1%	3	3 1.5	6.5	65.1%	<u>6 27.7%</u>
	Suppression	No-change	ŗ	5 8.8	3 4.0	-33.3%	-18.6%	3	11.6	5 4.9	-31.2%	5 11.4%		2 6.4	0.9	-75.8%	-46.2%	2	2 4.2	1.6	-59.0%	6 19.2%
		Time-locked	(כ				5	7.7	3.5	-35.8%	<mark>6</mark> 46.7%		2 8.7	3.5	-43.0%	74.9%	2	2 5.4	2.0	-46.8%	6 27.0%
	Buildup	No-change	-	7 6.3	5.0	8.1%	-4.7%	2	15.5	6.1	-36.8%	6 18.2%	ļ	5 3.2	3.3	6.6%	-15.5%	4	4 2.2	3.0	17.0%	6 31.2%
		Time-locked	(כ				5	4.7	2.9	-6.0%	6 47.2%		7 4.3	6.4	29.5%	72.9%	7	1 3.4	4.6	14.0%	6 30.6%
Normal	No-change	No-change		1 1.3	3 1.2	-5.0%	-2.5%	3	6.3	5.5	-5.5%	2.7%	()				C)			
		Time-locked	()				0						2 7.4	8.1	4.7%	-5.2%	2	2 7.3	7.6	-0.1%	6 -7.5%
	Enhancemen t	No-change	4	4 3.6	5 8.1	. 41.8%	-4.4%	2	0.6	5 3.7	61.6%	5.8%	:	3 1.1	. 3.7	54.1%	13.9%	1	L 2.C	3.2	22.4%	6 24.0%
		Time-locked	(כ				0						כ				C)			
	Suppression	No-change	:	1 1.6	5 0.3	-66.0%	8.0%	1	5.1	. 2.1	-41.1%	<mark>6</mark> 8.2%	:	1 3.4	0.9	-57.6%	-14.0%	2	2.8	0.9	-45.8%	6 -10.6%
		Time-locked	(כ				0						D				C)			
	Buildup	No-change	ļ	5 2.2	2 5.1	16.0%	-4.1%	3	3.2	3.4	8.1%	5 7.1%		3 1.5	5 1.5	16.8%	6.6%	2	2 3.1	2.1	-18.5%	6 5.0%
		Time-locked	()				0					:	1 7.6	8.1	3.3%	-5.5%	C)			

Table 2. Single-unit classification based on pathology, stimulation epoch pattern and inter-pulse pattern.

Discussions Implications of the time-locking

Systems/Circuits

Neuronal Ensemble Synchrony during Human Focal Seizures

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Time-locking - a measure of the susceptibility of the neuron to synchronization

Truccolo et al 2014:

- Fine temporal synchrony (<10 ms) might affect neuron's efficacy in driving downstream targets
- Temporal synchrony can lead to the formation of large-scale networks
- Fine temporal synchrony can induce changes in synaptic efficacy / effective network connectivity.

al., 2012; Jiruska et al., 2013). Furthermore, the temporal precision of synchrony at the level of single-neuron spiking (action potentials) has not been examined during human seizures, and is a critical issue for understanding the nature and mechanisms of epileptic seizures. Fine temporal (<10 ms) spike synchrony in a group of neurons might substantially affect their efficacy in driving downstream targets (Abeles, 1991; Kumar et al., 2010). In addition, temporal synchrony resulting from the entrainment of neuronal spiking into oscillatory activity can lead to the formation of dynamic large scale networks (Singer, 2011). Fine temporal synchrony can also induce changes in synaptic efficacy (effective network connectivity) via neuronal spike timingdependent plasticity (Dan and Poo, 2006). Challenges in singleneuron ensemble recordings during human seizures and in the statistical assessment of synchrony have posed difficult obstacles

Conclusions

- Time-locking is associated with pathological cortex.
- Only frequencies of 10 Hz and above result in significant timelocking.
- Higher frequencies (30 Hz) have an excitatory effect, particularly in pathological tissue.

This study highlights the firing rate properties of single units in epileptogenic cortex. The results have implications in understanding the basic mechanisms underlying epileptogenic networks and in modulating the neuronal activity through electrical stimulation.

Acknowledgments

We would like to thank Mihai Malîia, Alin Rasina, Bogdan Balanescu and Irina Popa for their contribution to this study.

Grant support: Romanian government UEFISCDI research grant PN-II-ID-PCE-2011-3-0240.

References

- 1. Barborica A, Donos C, Ciurea J, Rasina A, Balanescu B, Mindruta I. Stimulus Amplitude Effect In Time And Frequency On Responses To Single Pulse Electrical Stimulation In Stereoelectroencephalographic Studies, The 30th International Epilepsy Congress, Montreal, Canada, 23–27 June, 2013, Epilepsia, 54(S3):267–268, 2013.
- 2. David O, Woźniak A, Minotti L, Kahane P. Preictal short-term plasticity induced by intracerebral 1 Hz stimulation. Neuroimage. 2008 Feb 15;39(4):1633-46.
- 3. Hashimoto T, Elder CM, Vitek JL. A template subtraction method for stimulus artifact removal in high-frequency deep brain stimulation. J Neurosci Methods. 2002 Jan 30;113(2):181-6.
- 4. Meier R, Egert U, Aertsen A, Nawrot MP. FIND a unified Framework for neural data analysis; Neural Netw. 2008 Oct; 21 (8): 1085-93
- 5. Valentin A, Anderson M, Alarcon G, Seoane JJ, Selway R, Binnie CD, Polkey CE. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. Brain 2002;125:1709–1718.
- 6. van 't Klooster MA, Zijlmans M, Leijten FS, Ferrier CH, van Putten MJ, Huiskamp GJ. Time-frequency analysis of single pulse electrical stimulation to assist delineation of epileptogenic cortex. Brain 2011;134:2855-2866.
- 7. Wagenaar DA, Potter SM. Real-time multi-channel stimulus artifact suppression by local curve fitting. J Neurosci Methods. 2002 Oct 30;120(2):113-20.
- 8. Widrow B, Glover JR, McCool JM, Kaunitz J et al. Adaptive noise cancelling: Principles and Applications. Proc. IEEE, 1975;46(8):1151-1162