

Supplementary Online Content

Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy *JAMA Neurol*. Published online April 15, 2019. doi:10.1001/jamaneurol.2019.0658

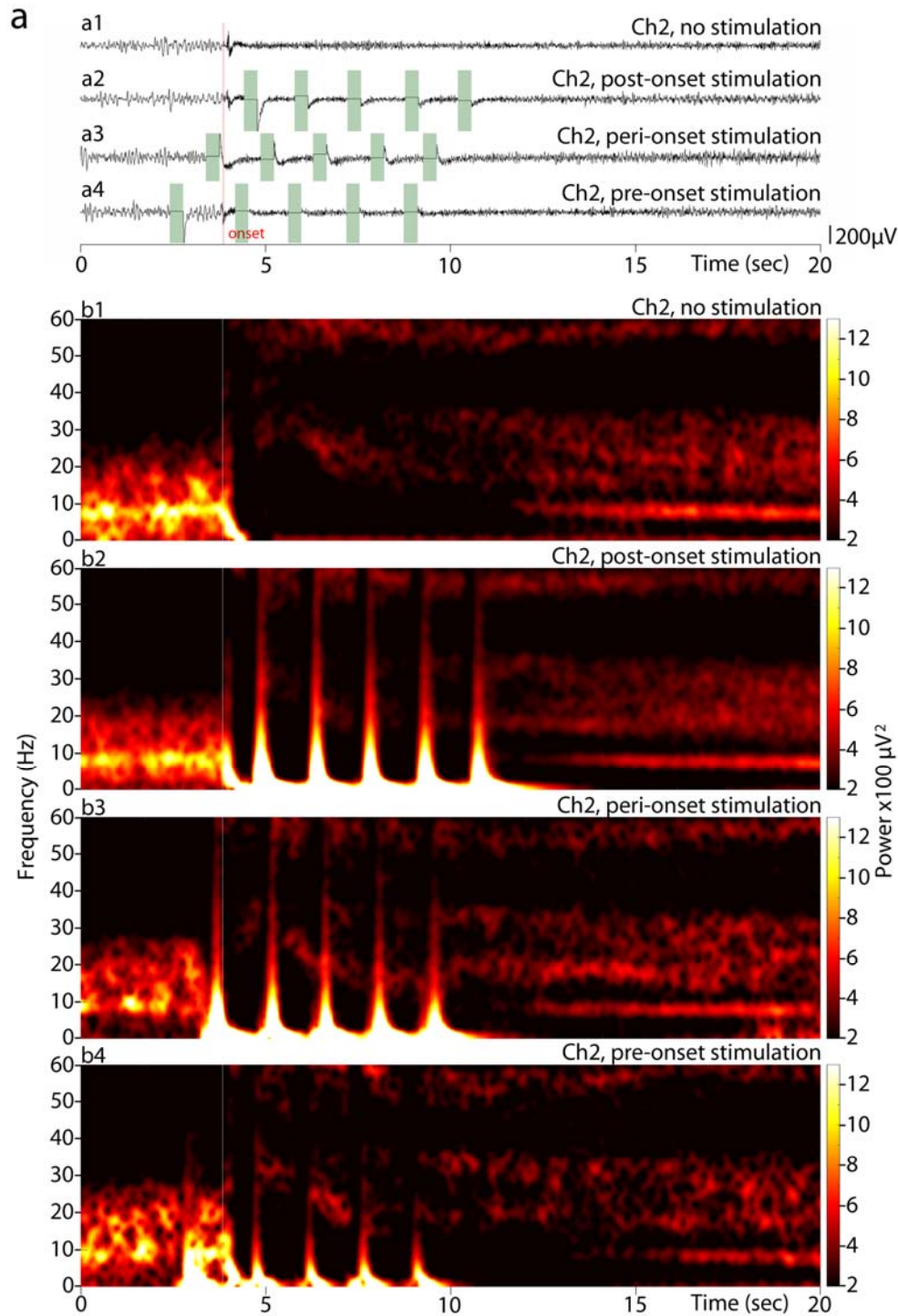
eFigure. Electrographic Seizure Patterns Relative to the Onset of the First RNS Stimulation Pulse

eTable 1. Patients, Closed-Loop Stimulation Effects, and Outcomes

eTable 2. Temporal Evolution of Direct and Indirect Modulation Effects

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Electrographic Seizure Patterns Relative to the Onset of the First RNS Stimulation Pulse



Visual evaluation of the ESP across patients resulted in four major clusters, regarding the relative timing between the onset and the application of the first stimulation pulse: (a) Raw RNS-derived ECOGs of patient 2 showing the post-onset, perionset and preonset stimulated electrographic events (a2-a4), along with a nonstimulated event for reference (a1). (b) Averaged time-frequency power graphs corresponding respectively to the above clusters of the raw ECOGs. Only the former two electrographic seizure pattern categories (nonstimulated and postonset stimulated events) were included and considered for processing in this study. Electrographic seizure pattern events with peristimulus and prestimulus onset were not dealt with, in order to maintain both the homogeneity of samples and the accuracy of the spectral averaging processes.

eTable 1. Patients, Closed-Loop Stimulation Effects, and Outcomes

PATIENT	AGE	SEX	IMPLANTATION		DIRECT STIMULATION EFFECTS		INDIRECT STIMULATION EFFECTS					OUTCOME (ENGL SCALE)
			SITES & PATHOLOGY	MONTHS	DIRECT INHIBITION (Onset week)	FREQUENCY MODULATION (Onset week)	SPONTANEOUS ATTENUATION (Onset week)	FREQUENCY MODULATION (Onset week)	COARSE FRAGMENTATION (Onset week)	FINE FRAGMENTATION (Onset week)	MEAN SEIZURE DURATION (Onset week)	
1	21	M	R Fronto-parietal PMG	6	X	X	X	Y (w0)	X	X	X	IIB SF: 98.2% SS: 33.3% SD: 0.0%
2	44	F	L Basal-temporal AVM	22	Y (w28)	Y (w21)	X	X	X	X	X	IVB SF: 0.0% SS: 0.0% SD: 0.0%
3	24	F	B Mesial-temporal No lesion	13	Y (w20)	X	X	X	X	X	X	IVB SF: 0.0% SS: 0.0% SD: 0.0%
4	40	F	B Mesial-temporal No lesion	10	X	Y (w2)	X	X	X	X	X	IVB SF: 0.0% SS: 0.0% SD: 0.0%
5	29	M	R Fronto-parietal PMG/Heterotopia	5	X	Y (w5)	X	Y (w9)	X	X	Y ↓ (w3)	IIB SF: 72.3% SS: 8.8% SD: 20.0%
6	24	F	B Mesial-temporal No lesion	15	X	X	X	X	X	Y (w60)	X	IVA SF: 0.0% SS: 26.3% SD: 15.7%
7	36	F	R Mesial-frontal No lesion	19	X	X	X	Y (w1)	X	X	Y ↓ (w12)	IB SF: 100.0% SS: 100.0% SD: 100.0%
8	40	F	L Fronto-parietal Heterotopia	9	Y (w4)	X	X	Y (w20)	Y (w19)	X	X	IIIA SF: 90.0% SS: 81.8% SD: 92.7%

9	32	M	B Mesial-temporal No lesion	8	X	X	X	X	X	X	Y ↑ (w7)	IVC SF: -11.4% SS: 6.6% SD: 50.0%
10	65	F	B Temporal No lesion	13	Y (w5)	X	X	X	Y (w8)	X	Y ↓ (w53)	IB SF: 100.0% SS: 100.0% SD: 100.0%
11	49	F	B Occipito-temporal Heterotopia	26	X	X	Y (w9)	X	X	X	Y ↓ (w81)	IIIA SF: 66.7% SS: 77.7% SD: 50.0%

Patients, closed-loop stimulation effects, and outcomes (Y: present, X: not present, ↑ = decrease, ↓ = increase, R: right, L: left, B: bilateral; Onset weeks refer to the time an effect was first observed after activation of RNS stimulation; Percentages in the Engel scale column represent reported reduction in seizure frequency (SF), severity (SS), and duration (SD)).

eTable 2. Temporal Evolution of Direct and Indirect Modulation Effects

PATIENTS	EFFECT TYPE	PE1 (weeks)	PE 2 (weeks)	PE3 (weeks)	PE4 (weeks)	PE5 (weeks)	PE6 (weeks)	PE7 (weeks)	PE8 (weeks)	PE9 (weeks)
Patient 1	Indirect frequency modulation	w1-w16 100%	w16-w24 100%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Patient 2	Direct inhibition	w5-w16 0%	w16-w26 0%	w26-w46 3%	w46-64 0%	w64-w73 0%	w73-w97 5%	n/a	n/a	n/a
	Direct frequency modulation	w5-w16 0.0%	w16-w26 100%	w26-w46 100%	w46-64 100%	w64-w73 100%	w73-w97 100%	n/a	n/a	n/a
Patient 3	Direct inhibition	w4-w9 0.0%	w9-w20 2%	w20-w29 15%	w29-w38 9%	w38-w47 2%	w47-w56 9%	n/a	n/a	n/a
Patient 4	Direct frequency modulation	w2-w16 100.0%	w16-w24 100%	w24-w31 100%	w31-w45 100%	n/a	n/a	n/a	n/a	n/a
Patient 5	Direct frequency modulation	w2-w22 50%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Indirect frequency modulation	w2-w22 50%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Seizure duration modulation	w2-w22 100%	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Patient 6	Fine fragmentation	w5-w16 0%	w16-w34 0%	w34-w43 0%	w43-w66 40%	n/a	n/a	n/a	n/a	n/a
Patient 7	Indirect frequency modulation	w5-w11 100%	w11-w15 100%	w15-w19 100%	w19-w24 100%	w24-w62 100%	w62-w71 100%	w71-w86 100%	n/a	n/a
	Seizure duration modulation	w5-w11 0%	w11-w15 25%	w15-w19 60%	w19-w24 50%	w24-w62 69%	w62-w71 73%	w71-w86 79%	n/a	n/a
Patient 8	Direct inhibition	w3-w19 44%	w19-w28 42%	w28-w43 38%	n/a	n/a	n/a	n/a	n/a	n/a
	Indirect frequency modulation	w3-w19 0%	w19-w28 0%	w28-w43 7%	n/a	n/a	n/a	n/a	n/a	n/a
	Coarse fragmentation	w3-w19 0%	w19-w28 19%	w28-w43 43%	n/a	n/a	n/a	n/a	n/a	n/a
Patient 9	Seizure duration modulation	w5-w14 71%	w14-w23 100%	w23-w37 100%	n/a	n/a	n/a	n/a	n/a	n/a
Patient 10	Direct inhibition	w3-w19 4%	w19-w24 8%	w24-w30 4%	w30-w43 6%	w43-w54 1%	w54-w90 1%	w90-w105 1%	n/a	n/a
	Coarse fragmentation	w3-w19 2%	w19-w24 1%	w24-w30 2%	w30-w43 5%	w43-w54 21%	w54-w90 70%	w90-w105 28%	n/a	n/a
	Seizure duration modulation	w3-w19 0%	w19-w24 0%	w24-w30 0.00%	w30-w43 0%	w43-w54 4%	w54-w90 3%	w90-w105 3%	n/a	n/a
Patient 11	Spontaneous attenuation	w3-w7 0%	w7-w16 8%	w16-w27 7%	w27-w42 13%	w42-w62 17%	w62-w71 10%	w71-w80 20%	w80-w98 4%	w98-w112 10%
	Seizure duration modulation	w3-w7 0.00%	w7-w16 0.00%	w16-w27 0.00%	w27-w42 0.00%	w42-w62 0.00%	w62-w71 0.00%	w71-w80 0.00%	w80-w98 28.57%	w98-w112 30.00%

Temporal evolution of direct and indirect modulation effects. The presence of each effect is quantified as a percentage of the total number of electrographic seizure patterns identified per programming epoch (PE) (n/a = not available).