Seizure onset zone connectivity during wakefulness and sleep studied through single pulse electrical stimulation during SEEG recordings

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Background

The seizure onset zone (SOZ) is defined as the area of the cortex that initiates clinical seizures. Considering the propagation pattern in the first seconds of the seizure, the epileptogenic zone (EZ) is revealed, being relevant for successful epilepsy surgery (Rosenow, Luders, 2001). Determination of the SOZ requires careful evaluation and correlation of all electric, anatomic and clinical data. In selected cases, depth electrode exploration (SEEG) is required and only the recording of spontaneous, unprovoked seizures allows the accurate identification of the SOZ. In some patients, invasive exploration disturbs the epileptogenic network and seizures fail to occur. In such cases, direct electrical stimulation might aid in the identification of the SOZ and EZ. Consindering that sleep is a provocative factor and favors epileptic discharges in standard EEG, the same should be observed in SEEG. There are currently no studies on the influence of sleep on SOZ connectivity.

Methods

We selected 8 epilepsy surgery candidates with refractory epilepsy and no lesions on cerebral MRI, explored by intracerebral depth electrodes as part of the presurgical protocol, at the Emergency University Hospital Bucharest, between 2016 and 2017. All patients signed an informed consent for participation and were evaluated for cognitive status, depression and sleep.

We performed single pulse electrical stimulation (SPES) protocol of the pairs of contacts that were used for SEEG recordings during wakefulness and sleep. SPES protocol consists of single pulses of 3 ms, at successive random current charge from 0.25 to 5 mA, in every frequency band between 0 and 1000, delivered at 15 seconds interval (Donos C. et.al., 2015) (Figure 1). Average early responses (ER) (Figure 2) obtained by stimulation, which are considered physiological (Valentin A. et.al., 2005), were processed and the difference in connectivity between wakefulness and sleep was analysed using average ER per cerebral structure, recorded in 62 contacts in individual montages.

We considered that connecivity between two structures was significant if the average ER per structure obtained by stimulation in SOZ pertained to the upper 25% of all the recorded responses. We also analyzed if there is a significant change in average structure response during sleep using t-test (significant $p<0.05$). Graphs displaying connectivity change of SOZ were generated.

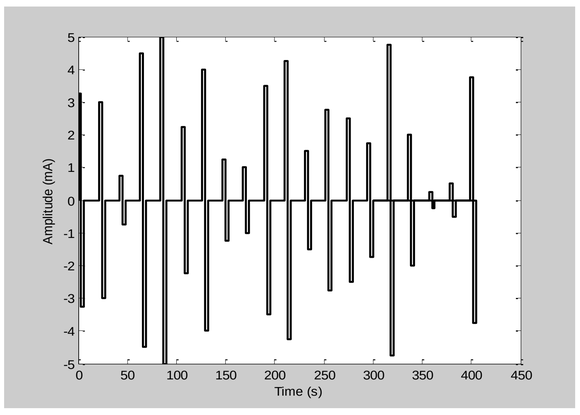

Figure 1: Single Pulse Electrical Stimulation (SPES)

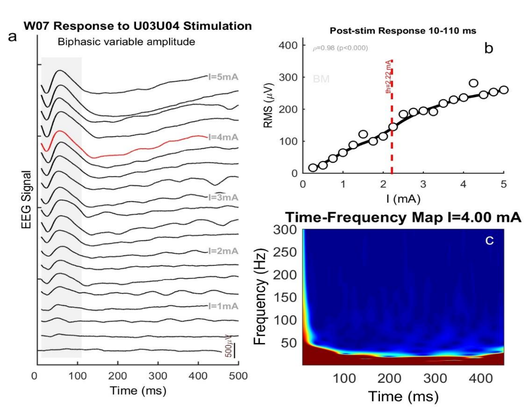

Figure 2: SPES Early Response (<100ms) analysis

Results

We analysed a series of stimulations from 8 patients (Table 1) implanted with 19 electrodes in the seizure onset zone, either in the left or right hemisphere. We stimulated a total of 28 pairs of contacts, each during wakefulness and sleep. SEEG depth electrode implantation differred for each patient, according to an initial electro-anatomo-clinical hypothesis. The seizure onset zone was different for each patient (Table 2).

Overall, in each patient, average ERs obtained during wakefulness were significantly greater than those obtained by stimulation during sleep ($p<0.001$). This relationship, though, is partially true for stimulation in the SOZ. The ER amplitudes obtained by SPES stimulation in the SOZ and recorded in all implanted brain structures were on average higher during sleep only in patients with nocturnal seizures

Looking at Figure 3, we observe in patients with daytime seizures a general decrease in connectivity bewteen SOZ and other structures, the greatest loss in amplitude ocurring within the SOZ itself, but maintaining an ample ER. In contrast, patients with nighttime seizures seem to have an increase in connectivity in almost all recorded structures, favoring neighbouring areas. Despite this, we identified constant, stong connectivity within the SOZ in mesial temporal epilepsy patients. In 4 patients, by stimulating the SOZ (amygdala and hippoccampus), the temporal pole was among the structures with a significant response only during sleep.

In the patients who were bilaterally implanted, the SOZ exhibits bilateral significant connectivity. During wakefulness, there is a greater number of bonds with ipsilateral structures, while during sleep the number greatly increases. A constant relationship stands, during both wakefulness and sleep, between MOFC and contralateral amygdala, irrespective of which is in the SOZ.

Table 1: Patients included in the study

ID	Sex	Age	Seizure fequency	Epilepsy	Lateralization	MoCA score	Pathology	Surgical Outcome
P1	M	38	5-6/week	orbitofrontal	L	27/31	FCD IIb	Engel Ia
P2	F	48	7-10/week	temporal mesial	L	26/30	FCD IIb	Engel Ia
P3	M	27	1/week	temporal mesial	L	28/30	FCD IIb	Engel Ia
P4	M	17	1-3/month	parietal operculum	R	30/31	not available	Engel Ib
P5	F	34	8-12/week	temporal mesial	L	23/31	FCD IIb	Engel Ia
P6	M	18	2-3/week	postcentral mesial	R	26/31	FCD IIa	Engel Ic
P7	F	34	5-6/week	temporal mesial	R	27/30	FCD IIb	Engel Ia
P8	M	21	3-4/week	postcentral mesial	R	29/30	FCD IIa	Engel IIb

Table 2: Patients' SOZ SPES stimulation early responses averaged for all brain structures

ID	Sex	Age	Epilepsy onset	Seizure timing	Implantation	SOZ	Best ER awake	Best ER sleep	Av ER awake	Av ER sleep	p
P1	M	38	18	Night	Bilateral	L MOFC	L ACC	L VLPFC	46.34	97.29	<0.001*
						L OF	-	-	-	-	-
P2	F	48	25	Day	L	L Hc	L PHG	L PHG	87.21	19.08	0.030*
						L PHG	L Hc	L Hc	62.17	22.44	0.085
						L E	L Hc	L Hc	106.37	20.38	0.032*
P3	M	27	10	Day	L	L A	L E	L Hc	70.82	29.34	0.022*
P4	M	17	14	Day = Night	R	R OpP	R aI	R aI	51.67	30.21	<0.001*
						R IPL	R aI	R aI	37.67	29.05	0.001*
P5	F	34	9	Day > Night	Bilateral	L A	L Hc	L VMPFC	61.52	46.22	0.039*
						L Hc	L E	L F	48.15	52.19	0.499
						L E	L Hc	R OpF	52.35	45.88	0.141
P6	M	18	6	Night	R	R MCC	R MCC	R pI	26.27	32.10	0.290
						R S	R pI	R S	22.01	39.35	0.014*
						R PCL	R pI	R preSMA	28.14	27.07	0.879
P7	F	34	20	Day	R	R A	R A	R Hc	246.44	35.33	0.296
						R Hc	R Hc	R E	108.60	34.85	0.149
						R E	R E	R Hc	270.98	34.19	0.099
P8	M	21	20	Night	R	R MCC	R MCC	R SPL	23.18	29.90	0.008*
						R S	R SPL	R SPL	23.35	25.90	0.236

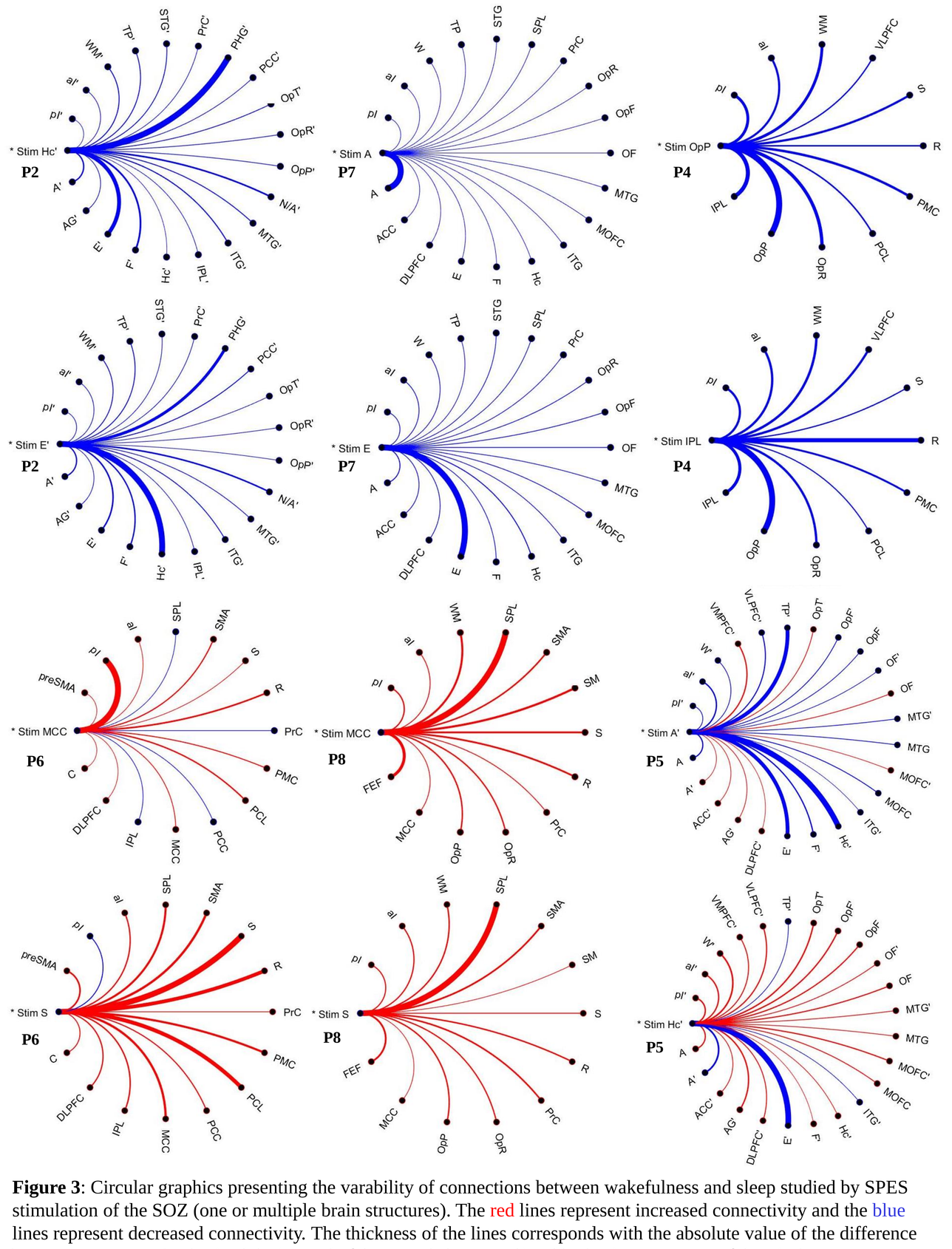

Figure 3: Circular graphics presenting the varability of connections between wakefulness and sleep studied by SPES stimulation of the SOZ (one or multiple brain structures). The red lines represent increased connectivity and the blue lines represent decreased connectivity. The thickness of the lines corresponds with the absolute value of the difference between average ERs obtained during wakefulness and sleep, mediated by brain structure. Left hemisphere structures are marked with '.

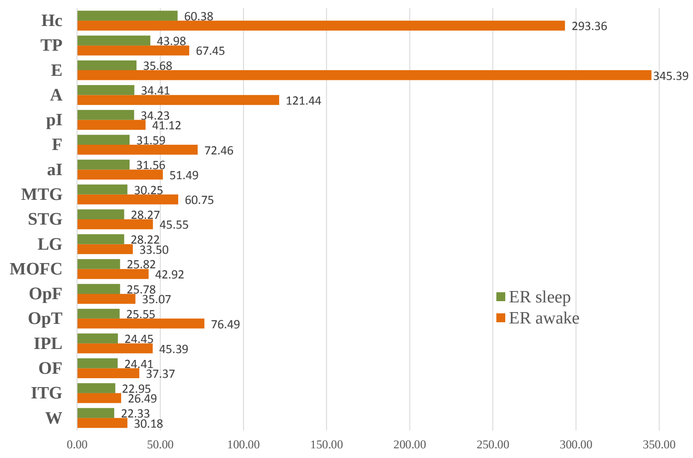

Figure 4: Amygdala (SOZ) SPES stimulation and resulting average ER awake vs. sleep in P3

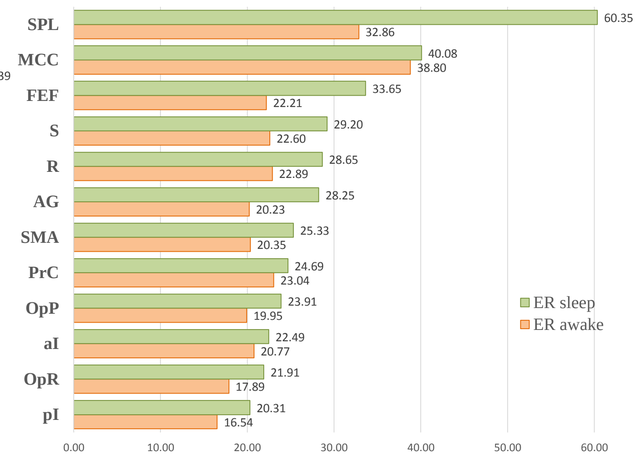

Figure 5: MCC (SOZ) SPES stimulation and resulting average ER awake vs. sleep in P8

Discussions

Interpretation of these results may be difficult because of different SEEG sampling among patients, offering only a limited view on SOZ connectivity. However, there are consitent, significant differences between average ER obtained during wakefulness in comparison with sleep in most of the recorded cerebral structures, indicating that sleep has a significant influence on SOZ connectivity.

The ERs obtained by stimulating the SOZ in the areas adjacent to SOZ are significantly inhibited during sleep in comparison with wakefulness, supporting evidence from previous studies that focal SOZ inhibits adjacent areas (Warren et. al. 2010).

The inner connectivity of the SOZ during sleep in patients with daytime seizures is enforced as opposed to a more widespread connectivity with remote structures during wakefulness. The opposite is observed in patients with nocturnal seizures, drawing attention on possible mechanisms of epileptogenicity and spread pattern differences.

There is an important number of contralateral connections that seem to be enforced during sleep, probably under the influence of the limbic system, giving indications on the speed of spreading and certain clinical features of seizures. Interhemispheric connectivity of the SOZ is a novel finding and might explain propagation patterns and false lateralization on scalp EEG.

We also identified constant, stong connectivity between the SOZ and other brain areas, irrespective of patient status (A-E, A-MOFC, MOFC-TP, Hc-F, MCC-preSMA, MCC-SPL, OpP-aI, S-pI, PCL-PrC). All these connections have been previously described in different studies, but this is the first time they are confirmed as constant during sleep.

Conclusions

Sleep has a significant influence on overall SOZ connectivity. SOZ inner connectivity is enforced during sleep in patients with daytime seizures, at the same time experiencing a great reduction in excitability. In patients with nighttime seziures, the SOZ tends to increase its connectivity with all adjacent areas. Contralateral connectivity of the SOZ is also enforced by sleep. These findings have important implications in epilepsy surgery. More studies are needed to confirm the presented results.

Acknowledgements

SEEG procedures and data collection supported by Romanian UEFISCDI research grant PN-II-ID-PCE-2011-3-0240

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