Mapping Cortical Excitability Using Single Pulse Electrical Stimulation in Stereoelectroencephalographic Studies

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Introduction

Single pulse electrical stimulation (SPES) has been shown to evoke a large variety of response types, including delayed responses (DR) (Valentin et al 2002, 2005) high-frequency oscillations (HFO) (Van't Klooster et al 2012), that could be used as epileptogenicity biomarkers. The identification of different response typologies require elaborate methods for detection of the signal features, that can only be partially automated.

We are aiming at investigating the value of early responses (ER) for the delineation of the epileptogenic networks. The amplitude of the raw signal over a fixed post-stimulation time window is used as primary input for the analysis (David et al, 2008), this approach allowing for an automated processing of the recorded signal.

The ER are recorded intracranially on depth electrodes implanted stereotactically. Stereoelectroencephalography (SEEG) allows for the exploration of deep brain structures, including novel areas (Kahane, 2012), with good 3D spatial sampling.

Among other stimulation protocols, SPES has the advantage of probing brain excitability while causing minimal disturbance of the network, as a result of the mininal charge injected over time, therefore rarely resulting in afterdischarges or clinical responses.

The excitability of cortical areas can be assessed from the stimulus-response curves, that has been shown to be a correlate of seizure onset zone (SOZ) (Enatsu et al, 2012). We are therefore applying a stimulation protocol where the amplitude varies for each applied pulse, allowing for the calculation of the stimulation intensity thresholds.

While SPES has been previously used with electrocorticography (ECoG) and non-stereotactically implanted depth electrodes, we aim at integrating the stereotactic coordinate information with the amplitude of the early responses to generate exact maps of excitability for each investigated patient.

Methods

12 Patients with refractory temporal lobe epilepsy referred to pre-surgical evaluation using SEEG method have been included in this study.

Patient	Sex	Age	Pathology	Lateralization	Localization	Num Electrodes	Implantation Side
1	F	37	Type I cortical dysplasia	L	Temporal, mesial	12	L
2	F	32	Type I cortical dysplasia	L	Temporal, mesio-basal	11	L
3	F	41	Hippocampal sclerosis	R	Temporal, mesial	11	R
4	M	27	Type I cortical dysplasia	L	Temporal, middle temporal gyrus	9	L
5	M	46	Hippocampal sclerosis	L	Amygdala	12	L
6	F	17	Type II cortical dysplasia	L	Premotor dorsolateral	11	L
7	M	39	Not operated on	L	Occipito-temporal basal	16	B
8	M	47	Dysembryoplastic neuroepithelial tumour	L	Temporal, middle temporal gyrus	11	L
9	F	40	Not operated on	L	Prefrontal	11	L
10	F	35	not operated on	R	Amygdala	12	B
11	F	24	not operated on	R	Rolandic	15	R
12	M	24	not operated on	R	Occipito-temporal basal	14	B

Table 1. List of investigated patients. DNET - Dysembryoplastic neuroepithelial tumour

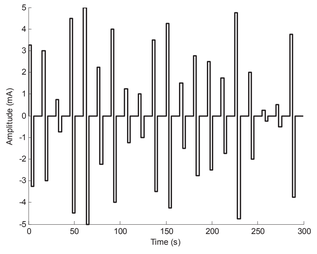

Figure 1. Stimulation protocol using variable-amplitude pulses

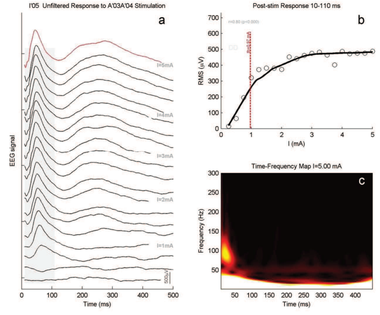

Figure 2. Analysis of the insular responses to stimulation of left amygdala in patient 10: a) a raster of EEG traces aligned to the stimulation pulses, sorted by amplitude; b) stimulus-response curve; c) time-frequency map for the selected trace (highlighted in red). The 3-D location of the electrodes is shown in figure 5.

Single-pulse stimulation protocol included a sequence of 20 biphasic pulses having 3ms pulse width, 15s inter-pulse interval and variable amplitude in the 0 to 5 mA range. To decouple time and amplitude factors in our analysis, we have applied the pulses in a pseudo-random sequence, as illustrated in fig. 1, using a programmable stimulator (Guideline LP+, FHC Inc, Bowdoin, ME) that allows definition of complex waveforms. Stimulation was applied on 9-30 contact pairs in each patient.

The data was sampled at 4096 Hz and recorded using Nicolet 64-channel wireless amplifier, with no filtering. We calculated the fast responses as the standard deviation of the raw signal (David et al, 2008), which is identical to the root-mean square (RMS) of the AC component, over a 100ms window following each stimulation pulse. In order to exclude the stimulation artifacts, the first 10msec after the stimulus application were excluded from the analysis. Delayed (DR) and high-frequency responses (HFO) have been analyzed in a different study (Donos et al, 2013). Data was analyzed using Matlab (Natick, MA)

Stimulus-response curves were calculated for each contact as illustrated in figure 2. Data points were fitted using LOWESS (locally-weighted scatterplot smoothing) non-parametric regression. We calculated a 50% activation threshold based on the stimulus-response fitted curve. Pearson's correlation coefficient was calculated for each curve, and only the contacts exhibiting a significant ($p<0.05$) correlation were included in the analysis. By using the pseudo-random amplitude sequence, any buildup of the activity in time would result in a non-significant correlation between stimulus amplitude and response , therefore such situations would be automatically excluded from our analysis.

We used the third quartile value of pooled responses recorded for all stimulated sites as a threshold for calculating the individual contact activation (fig 3). We calculated the number of contacts that were activated for each stimulated site and the mean activation thresholds (fig 4).

Using the stereotactic coordinate position of each contact and co-registration information from the surgical planning software (Waypoint Navigator, FHC Inc, Bowdoin, ME), we were able to build 3D ER amplitude maps for each patient. Mean response amplitude was represented using a colormap blended with the patient's MR scans. Maximum intensity projections (MIP) of the responses were created, co-registered with the patient's MRI.

Two type of functional maps were created: 1) outbound activation maps, showing the mean responses on all contacts, by stimulation location and 2) inbound activation maps, showing the responses on each recorded contact, averaged over all stimulations on different contacts.

Results

We will first illustrate the steps for calculating ER, stimulus-response curve, activation thresholds, number of activated contacts for patient 10, that based on the standard SEEG investigation was found to have a SOZ located in the right amygdala, with the contralateral amygdala having a high epileptogenicity as well. Bilateral implantation was required due to a non-lesional MRI as well as non-lateralizing semiology and scalp video-EEG monitoring.

The ER in the anterior insular cortex as a result of applying a SPES sequence of 20 pulses to the left amygdala, sorted by increasing value of the intensity is shown in figure 2a. The stimulus-response curve reaches a plateau at currents greater than 2 mA. The 50% activation threshold was 0.97mA. The mean response amplitude of all contacts in the SEEG montage is shown in figure 3a. Same data, but sorted by response amplitude, is shown in fig. 3b, with a histogram of the response amplitude distribution on top. For the stimulation of contralateral (R)amygdala, results are shown in panels c and d of figure 3.

Contact	Hemisphere	Structure Abbrev	Structure
H'02	L	AC	Anterior Cingulate
H'01	L	AC	Anterior Cingulate
H'11	L	PHTVL	Ventro-Lateral Prefrontal
H'12	L	PHTVL	Ventro-Lateral Prefrontal
O'01	L	MOF	Medial Orbito-Frontalis
O'02	L	MOF	Medial Orbito-Frontalis
D'11	L	IFG	Inferior Frontal Gyrus
D'12	L	IFG	Inferior Frontal Gyrus
A'01	R	A	Amygdala
A'02	R	A	Amygdala
A'03	R	A	Amygdala
A'04	R	A	Amygdala
A'11	R	MTG	Middle Temporal Gyrus
A'12	R	MTG	Middle Temporal Gyrus
A'13	R	MTG	Middle Temporal Gyrus
B'02	R	PHG	Parahippocampal Gyrus
B'03	R	PHG	Parahippocampal Gyrus
B'11	R	ITG	Inferior Temporal Gyrus
B'12	R	ITG	Inferior Temporal Gyrus
B'13	R	MTG	Middle Temporal Gyrus
B'14	R	MTG	Middle Temporal Gyrus
M'01	L	WM	White matter
M'02	L	WM	White matter
M'03	L	PHTVL	Dorso-Lateral Prefrontal Gyrus
M'04	L	PHMD	Prefrontal, Middle Frontal Gyrus
M'05	L	I	Insula
M'06	L	I	Insula
I'01	R	I	Insula
I'02	R	I	Insula
I'03	R	PHTVL	Dorso-Lateral Prefrontal
I'04	R	PHTVL	Dorso-Lateral Prefrontal
H'01	R	AC	Anterior Cingulate
H'02	R	AC	Anterior Cingulate
H'04	R	PHTVL	Dorso-Lateral Prefrontal
H'03	R	PHTVL	Dorso-Lateral Prefrontal
O'01	R	MOF	Medial Orbito-Frontalis
O'11	R	OF	Orbitofrontal
O'12	R	OF	Orbitofrontal
I'05	L	I	Insula
I'06	L	I	Insula
I'07	L	I	Insula
I'08	L	I	Insula
I'09	L	I	Insula
I'10	L	PHTVL	Dorso-Lateral Prefrontal
I'11	L	PHTVL	Dorso-Lateral Prefrontal
A'01	L	A	Amygdala
A'02	L	A	Amygdala
A'03	L	A	Amygdala
A'04	L	A	Amygdala
A'11	L	MTG	Middle Temporal Gyrus
A'10	L	MTG	Middle Temporal Gyrus
A'13	L	MTG	Middle Temporal Gyrus
B'01	L	PHG	Parahippocampal Gyrus
B'02	L	PHG	Parahippocampal Gyrus
B'03	L	PHG	Parahippocampal Gyrus
B'04	L	PHG	Parahippocampal Gyrus
B'12	L	MTG	Middle Temporal Gyrus
B'13	L	MTG	Middle Temporal Gyrus
M'01	R	AC	Anterior Cingulate
M'04	R	PMD	Prefrontal, Middle Frontal Gyrus
M'05	R	PMD	Prefrontal, Middle Frontal Gyrus

Table 2. List of electrode contact locations for patient 10.

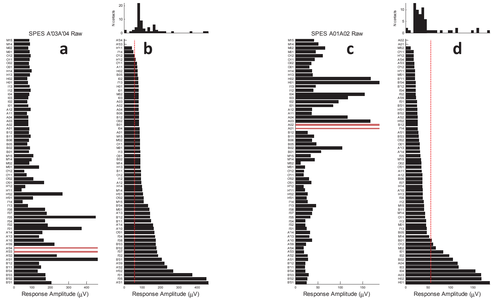

Figure 3. Bar chart of the mean response amplitudes for stimulating the left (a,b) and right (c,d) amygdala.

The histogram of the number of activated contacts shows preferential activation of areas presenting elevated epileptogenicity or being strongly connected with those areas: left amygdala(A'01-A'04), superior frontal gyrus (I'13), as well as SOZ and epileptogenic zone (A03). The results might reflect the network involved in propagation, not just SOZ location.

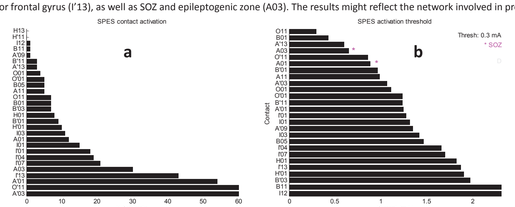

Figure 4. Contact activation and corresponding thresholds for SPES in patient 10. a) Number of contacts activated for each stimulated location; b) the mean activation thresholds for stimulations in panel a.

3-D maps of the outbound activation in the same patient are shown in figure 5. For the purpose of this representation, the mean response amplitude was represented, which results in smoother displayed maps for low number of stimulated contacts, as was the case in our first patients. While stimulation of the amygdala contralateral to SOZ evokes higher outbound responses, inbound activation maps show that the right amygdala (SOZ) was more excitable, as shown in fig. 6.

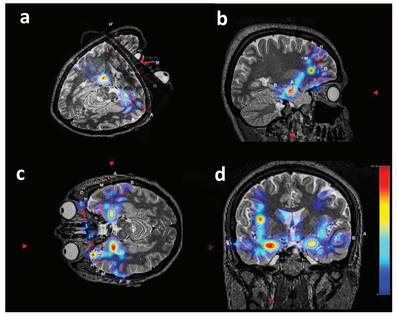

Figure 5. 3D outbound activation maps for patient 10, expressed as the mean amplitude of responses on all contacts, for each stimulation location. a) 3-D view of the maps, blended with MRI scans; b,c,d) MIP projections of the activation on sagittal, axial and coronal MRI views. SOZ contacts are marked using magenta circles.

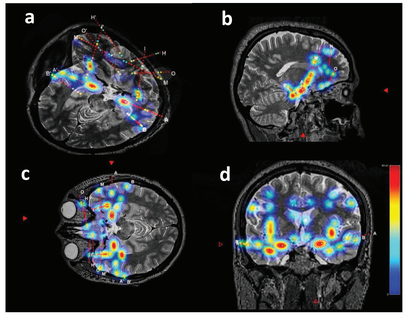

Figure 6. 3D inbound activation maps showing mean evoked responses, by location of recording, regardless of the stimulation location, for patient 10. a) 3-D view of the maps, blended with MRI scans; b,c,d) MIP projections of the excitability on sagittal, axial and coronal MRI views. SOZ contacts, marked using magenta circles.

The activation and excitability maps provided complementary information that was convergent with the SOZ and associated epileptogenic networks, as illustrated in fig 7 for four more patients.

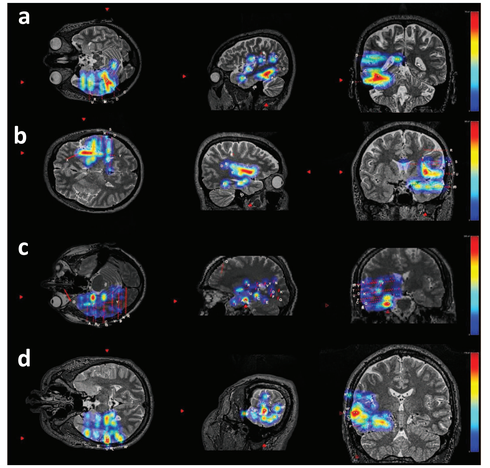

Figure 7. Excitability maps of responses to SPES (as in fig 6) for patients 2, 3, 5, and 8.

Patient	Stimulated Contact Pairs	Highest N of Activated Contacts in SOZ	Lowest Activation Threshold in SOZ
1	9	Y	Y
2	14	Y	Y
3	20	Y	Y
4	12	Y	Y
5	9	Y	Y
6	13	N	N
7	22	Y	Y
8	17	N	N
9	30	Y	Y
10	28	N	Y
11	29	Y	Y
12	29	Y	N
		75%	75%

Table 3. Number of stimulated contact pairs in each patient. The correlation between outbound activation (as illustrated in fig 4a) and SOZ location is in third column. The fourth column illustrates the correlation between lowest activation threshold (as illustrated in fig 4b) and the SOZ location.

Conclusions

ER maps have been shown to reveal pathological information. There are no stereotyped responses for stimulation of the same areas across patients.

3D maps of activation and excitability can provide valuable complementary information to recording spontaneous activity and responses to standard stimulation protocols for highlighting the epileptogenic network, therefore reducing the duration of the invasive monitoring phase.

Exact 3D maps for each patient were built by integrating the stereotactic location of each contact with the early responses evoked by SPES. To our knowledge, this is the first report of stereotactic SPES, that can be considered as a new type of functional tractography (David et al, 2013)

Activation and excitability maps provide two different points of view over the epileptogenic networks, for a better understanding of the mechanisms of the seizure initiation and propagation.

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