Modulating the Intracranial High-Frequency Stimulation Waveform in Conjunction with Nonlinear Tissue Response Allows Recovering the Physiological Responses During Stimulation

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Introduction

Responses to intracranial stimulation allow to unambiguously determine the causal interactions between brain areas (Friston, 1994), such that effective connectivity within the brain can be calculated (Entz et al., 2014; Donos et al., 2016a).

The main barrier in the way of analyzing the responses during high-frequency stimulation is the inability of existing stimulation artefact cancellation methods to completely differentiate between artifacts and physiological responses.

Instead of attempting to recover the responses from recordings marred by the stimulation artifact, we suggest an approach where the electrical stimulation waveform is modulated in such a way that the physiological responses can be disambiguated from the artefactual ones.

Specifically, we introduce the *alternating polarity* (AP) 50 Hz biphasic stimulation protocol, where the phase of each pulse is inverted from pulse to pulse. For such a stimulation pattern, all artefactual responses that propagate through volume conduction, capacitive coupling or electromagnetic interference, will follow the alternating polarity of the stimulation waveform. However, the axonal propagation of the signals between brain areas will always take place with the same polarity, regardless of the polarity of the signal that evokes the responses, as illustrated for instance in the figure 3f of a previous study of ours (Donos et al., 2016b). This difference in the polarity of the physiological and artefactual responses will allow their discrimination.

Methods

We have applied a modified 50Hz stimulation protocol for performing functional mapping in 4 patients undergoing presurgical evaluation for drug-resistant frontal lobe epilepsy. A total of 54 electrodes (16/19/11/8) (DIXI Microtechniques, Besancon, France) were implanted using a StarFix customized stereotactic frame (FHC Inc, Bowdoin, ME) (Yu et al., 2018) (3 patients) and Leksell frame (Elekta, Stockholm, Sweden) (1 patient), as shown in Figure 1. The patient gave their informed consent and contacts where DES was applied were chosen on clinical grounds (functional and epileptogenicity mapping).

Using a programmable clinical stimulator capable of generating complex or arbitrary waveforms (Guideline4000LP+, FHC, Bowdoin, ME), we have designed a stimulation protocol in which the polarity of the pulses in a 50Hz biphasic train used for performing functional stimulation in patients undergoing SEEG investigations, is inverted every pulse, as shown in Figure 2.

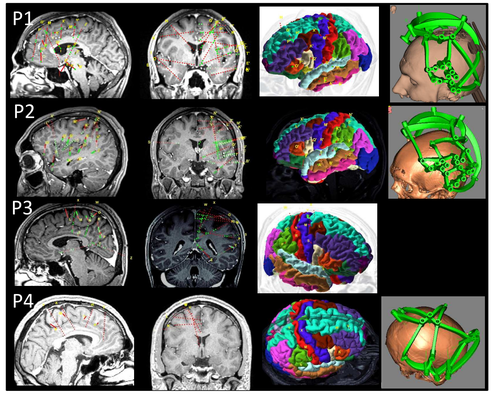

Figure 2. a-c) axial, sagittal and coronal views of the planned trajectories. Only left trajectories have been used; d) 3D view of the trajectories; e) position of the electrodes on the cortical surface reconstruction; f) customize stereotactic platform used for the implantation of the electrodes

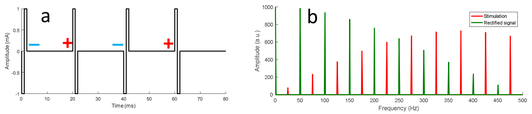

Figure 1. a) Alternating polarity stimulation waveform. Constant current biphasic pulses, f=50Hz, pulse duration t=1ms, I=0.25 – 3mA.b) Frequency spectrum of the stimulation waveform (red) and of a rectified version(green)

The AP waveform can be considered as a normal 50Hz train, that is modulated with a 25Hz square waveform having an amplitude +/-1. The spectral properties of the AP waveform can be inferred from the modulation theorem in the Fourier analysis:

$$\mathcal{F}\{\cos(\omega_0 t)\cdot f(t)\} = \frac{1}{2}[F(\omega-\omega_0)+F(\omega+\omega_0)]$$

Modulation → 50 Hz → 75 Hz, 25 Hz

The effect of such a modulation of a 50Hz train is the appearance of side frequencies at 25Hz and 75Hz, but, most importantly, the disappearance of the original 50Hz frequency. As the neural tissue response is nonlinear, i.e. has same polarity on every pulse, with a repetition rate of 50Hz, the spectral content of the physiological responses will have a line at the fundamental frequency of 50Hz. Several harmonics will be present for both the linear responses and non-linear responses, but they will never overlap.

The responses to AP stimulation were processed through the following steps, as illustrated in Figure 3:

- start of all stimulations were manually marked
- two 1-second epochs, before and during stimulation, were used for calculating the baseline R_B and response to stimulation R_S.
- the baseline and response signals were filtered in the [48 Hz – 52 Hz] range and up to 5th order harmonics using an ideal filter.
- responses that were non-significantly modulated by stimulation (p>0.05, Mann-Whitney U-test between multiple 0.1s epochs, 50% overlap, of the response and baseline intervals), exhibited afterdischarges or resulted in amplifier saturation were excluded.
- the RMS of the filtered signals was calculated to obtain R_B and R_s values, based on which the response to simulation R was calculated:

$$R = R_S - R_B$$

- the responses to stimulation on all recorded channels were represented as bar graphs, circular graphs and 3D color maps projected on patient's anatomy

To highlight the activation of specific pathways when a clinical symptom was elicited, we compared the responses for the stimulation that evoked a symptom (SYM), with the responses that did not evoke a clinical symptom (NS), as shown in Figure 4. We have calculated an activation factor (AF) of the responses on each channel by subtracting the current-normalized SYM and NS responses:

$$AF = R^{SYM}/I^{SYM} - R^{NS}/I^{NS}$$

For each stimulation site that evoked a clinical symptom, we have represented the activation factors for the set of recorded contact as circular graphs (as in Figure 5) or in 3D.

Results

A total of 4752 EEG responses, of which 2571 were significant, evoked by stimulation of 135 contact pairs were analyzed. Stimulation evoked 14 types of clinical symptoms at threshold currents lower or equal to 3 mA without associated after discharges, as listed in Table 1.

Symptom	Patients	Stimulations	Responses	Significant Responses
auditory hallucination	1	2	68	52
auditory illusion	1	3	101	57
autonomic	2	5	194	109
complex somatosensitive	2	16	565	317
dysarthria	2	14	507	301
elementary motor	3	40	1360	743
elementary somatosensitive	4	22	803	484
executive function	1	4	156	60
grimace	1	2	78	43
language	1	1	29	13
sensory	1	4	116	57
simple visual hallucination	2	10	336	127
simple visual illusion	1	6	230	92
vestibular	1	6	209	116

Table 1. List of clinical symptoms evoked by AP stimulation

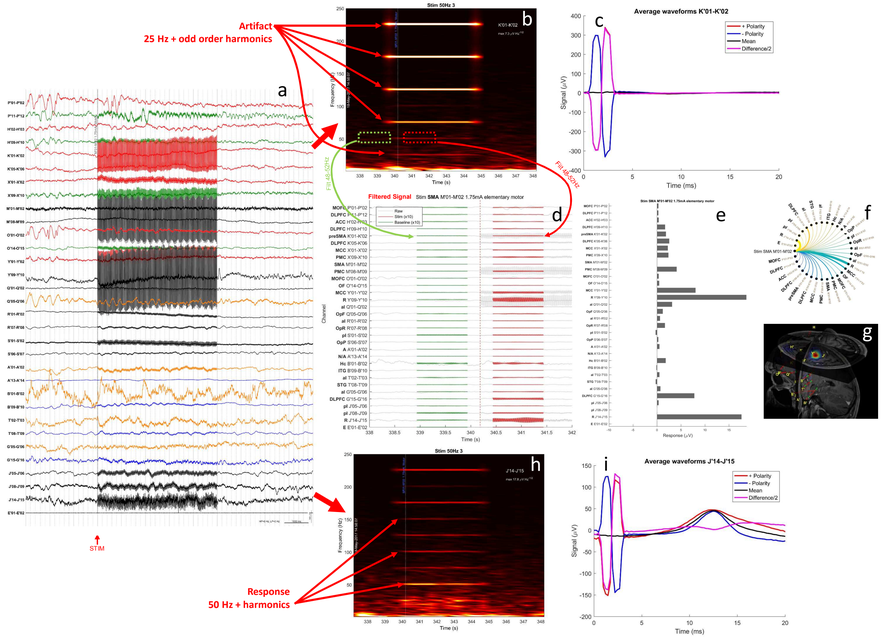

Figure 3. Illustration of responses to a single stimulation, as well as data analysis workflow. Stimulation of supplementary motor area (SMA) evokes a combination of artefactual and physiological responses on different contacts. The average waveforms of artefactual components have a mean over positive and negative pulses close to zero, and a fundamental frequency of 25 Hz, while the physiological components have a mean different from zero and a frequency of 50 Hz, occurring on every pulse, regardless of its polarity.

A typical recording of the responses to the stimulation of supplementary motor area (contact pair M'01-M'02), as well as the workflow for analyzing and visualizing data is shown in Figure 3. Two contact pairs were selected for illustration of a high artifact but small response (K'01-K'02) and of a larger response (J'14-J'15). Time frequency maps and average waveforms for the two selected contacts were plotted. The frequency spectrum of the recorded signal is in agreement with the prediction of the theoretical analysis (Fig. 1b), with non-overlapping lines at [25, 75, 125, 175, …] Hz for the artefact and [50, 100, 150, 200 …] Hz for the response. The average waveforms on J'14-J'15 illustrate the nonlinear responses to electrical stimulation, where same-polarity responses are observed regardless of the polarity of the stimulation pulses.

By comparing the responses evoked by stimulation levels eliciting a clinical symptom to the responses below the clinical threshold, we were able to evidence the selective recruitment of specific connections between brain areas, associated with a particular response. As an example, in figure 4 we illustrate the recruitment of a connection between R (Y'07-Y'08), SMA (M'01-M'02) and another region of the Rolandic cortex (J'14-J'15). The increase of the response in M'01-M'02 by a factor of ~5 exceeds the increase of the current from 0.5 mA to 1.75 mA, and a new connection (J'14-J'15) is activated.

Normalizing with the current level and subtracting the responses results in a set of activation factor values that is represented as a circular diagram in Figure 5, for the same stimulation site. This representation is indicative of the network connections that have been selectively activated at stimulation levels eliciting a specific response.

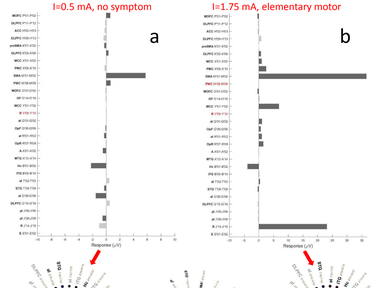

Figure 4. Difference in responses for subclinical levels of Rolandic cortex (R – Y'07-Y'08 pair) stimulation (I=0.5mA) and levels (I=1.75mA) that evoked elementary motor signs in patient 1.

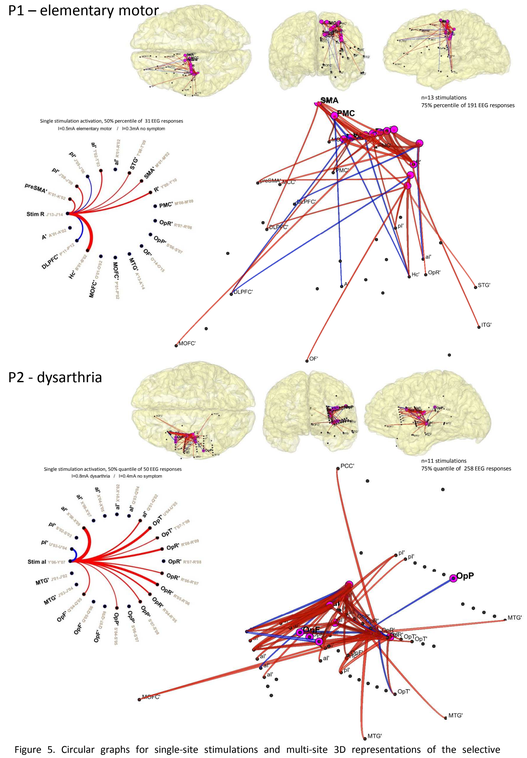

Figure 5. Circular graphs for single-site stimulations and multi-site 3D representations of the selective recruitment of connections associated with clinical effects. The thickness of the lines is proportional to the value of the activation factors (AF) and the color indicates the sign of the AF (red – positive, blue – negative).

Conclusions

By modulating the properties of the stimulation waveforms, in conjunction with the nonlinear response of the tissue to electrical stimulation, we were able to recover the physiological responses during the course of the stimulation train.

This method allowed us to evidence the activation of specific pathways in the brain when a clinical symptom is evoked by electrical stimulation.

Acknowledgments

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