BRAIN RESPONSE TO VAGUS NERVE STIMULATION TO IDENTIFY HOW EACH EPILEPTIC PATIENT COULD BENEFIT FROM A NEUROSTIMULATOR AS A TREATMENT

Supervising staff

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Context

Epilepsy is a neurological disease affecting 50 million people worldwide associated with increased mortality, stigma, psychiatric co-morbidity, and high economic costs. The world health organization characterizes epileptic seizures as: "*Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions*" (World Health Organization 2023).
In the patients diagnosed with epilepsy (representing an active incidence of 4/8 people over 1000 (Brodie et al. 2012)), one-third do not respond to epileptic drugs or partially without controlling the seizures and are classified as refractory epileptics. Vagus nerve stimulation (VNS) is an adjunctive treatment for refractory epilepsy in patients who are unsuitable candidates for anti-epileptic drugs or resective surgery. VNS uses an implanted pulse generator that delivers trains of electrical pulses to the left cervical vagus nerve. Although widely used, two-thirds of these implanted patients present an insufficient response or an absence of response to VNS (Ben-Menachem 2002). The identification of biomarkers to assess VNS efficacy pre-operatively would be crucial to reduce the number of non-responders.

In this context, our department, in collaboration with the Institute of NeuroScience (IoNS) at the Cliniques Universitaires of UCLouvain is aiming to develop new ways to assess clinical response to VNS prior to device implantation. The analysis of the evoked response potential (ERP) presented in this project could offer new possibilities to assess VNS responsiveness.

As shown in Figure 1, P300 is the positive peak deflection appearing at 300 ms in an ERP, classically elicited using an "oddball paradigm". The oddball paradigm consists of a series of stimuli, either visual or auditive, which are embedded target stimuli with a low presentation probability. The patient is asked to only recognize the stimuli, eliciting a brain response recorded by an electroencephalogram (EEG).
Recently, P300 has been investigated as a biomarker in people implanted with VNS devices by various works. On the one hand, P300 amplitude has been shown to be smaller in VNS responders prior to therapy when the device is turned ON (Hödl et al. 2020). On the other hand, patients' responses to VNS show an increase in P300 after therapy (> 18 months after implantation) when the device is turned ON (De Taeye et al. 2014). An example of such waveforms is shown in the next figure.

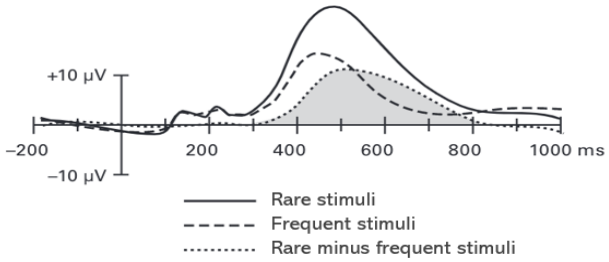

Figure 1: general principle behind P300 time-domain waveform analysis, adapted from (Luck 2005). *The data was not collected from true EEG recordings but instead shows a scheme of the brain response to rare and frequent stimuli.*

Various pre-processing steps are applied to the raw recordings to extract “epochs” (timeframes of typically 1200 ms containing the patient’s electrical brain response to one stimulus) before averaging them to obtain the mean differential waveform.

ERP P300 analysis in epileptic patients implanted with VNS stimulating device is an emerging field in literature, although already widely used in neuroscience. Experimental design, recording parameters, post-processing, and metrics all influence to some extent the resulting waveform.

Work

Our group already developed a framework to evoke and record P300 during three experimental conditions (Figure 2): 1. “VNS OFF”: when the VNS is turned completely OFF, 2. “VNS Low”: when the VNS is turned ON, 3.” VNS Low”: only when the VNS is actively stimulating, as illustrated in Figure 2.

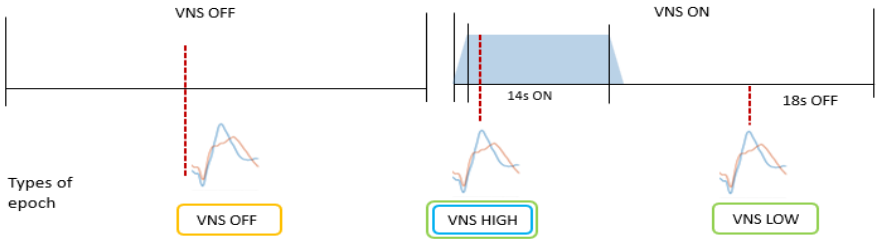

Figure 2: VNS stimulation consists of bursts of 500 or 250 µs stimulation pulses regrouped in the condition ON of stimulation duty cycle (here 14 s) followed by an OFF duration (here 18s). A simulation duty cycle is the ratio of the ON/OFF period. The current experimental setup allows eliciting the oddball paradigm under three different conditions.

This research project aims to implement different metrics to determine how the P300, based on the current framework available at the department, differs in responders from non-responders. Beyond the amplitude and latency of the P300, brain connectivity analysis is an emerging tool based on graph theory in the analysis of P300. Already intensively used to evaluate how highly specialized brain regions communicate with each other; recent works have exploited its use in the scope of P300 ERP analysis in healthy subjects.

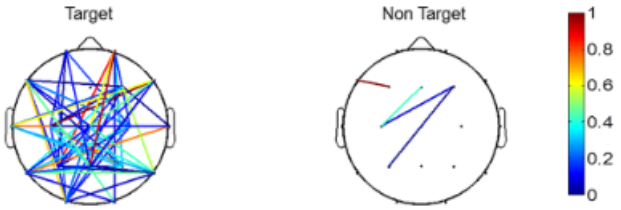

Figure 1. Representation of a brain connectivity network (Kabbara et al. 2016). *This graph was computed from EEG data from one patient, its nodes are the electrodes, and its associations were estimated using phase synchronization measure (here PLV), a measure quantifying the consistency of phase differences between the time series recorded at the considered electrodes). The association strengths range from 0 (no connectivity, in blue) to 1 (high connectivity, in red).*

Major steps in this work include:

- Familiarization with signal processing applied to evoked response potential and physiological background underlying ERP elicitation
- Familiarization with brain functional connectivity applied to evoked response potential and physiological background underlying ERP elicitation
- Exploring how the data processing parameters influence the P300 waveform in time-domain analysis
- Implementing a framework for brain connectivity analysis using different association metrics
- Analyzing the statistical differences between sets of P300 ERP in VNS epileptic responders and non-responders

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