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Predicting success of vagus nerve stimulation (VNS) from interictal EEG

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ABSTRACT

Purpose: Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy in numerous patients, however, not in all. It is still not possible to predict which patients will profit from VNS. In this pilot study, we explore predictive interictal EEG features for seizure reduction after VNS.
Methods: 19 Patients with medically refractory epilepsy and an implanted VNS system were included. Interictal EEG registrations, recorded before implantation, were retrospectively analysed. A quantative symmetry measure, the pair wise derived brain symmetry index (pdBSI), was tested to predict VNS outcome. Reduction in seizure frequency was used to define the responders.
Results: 10 Patients did respond to VNS, of whom 7 patients had a seizure reduction of at least 50% in a follow-up period of 2 years. On average, we find higher pdBSI values for delta, theta, alpha and beta bands for non-responders than for responders. The average pdBSI of the theta and alpha bands could significantly discriminate between responders and non-responders.
Conclusion: In this study, quantifying EEG symmetry using the pdBSI shows promising results in predicting the reduction of seizure frequency after VNS treatment.

1. Introduction

Vagus nerve stimulation (VNS) has shown to be an effective treatment for epilepsy in numerous patients. Most long-term studies that were done to assess the efficacy of VNS concluded that a more than 50% seizure reduction was accomplished in 20–55% of the patients after treatment for six months to six years.[1–3] According to Janszky et al.,[4] 0–24% of the medically refractory patients treated with VNS becomes seizure free.

Despite the growing application of VNS, it is still not possible to predict which patients respond to what extent to VNS therapy. Determining the success of VNS is important to counsel patients and give them information about the expected seizure reduction. Potential responders might not need to try other kinds of therapy before they receive an effective VNS system and on the other hand, a low likelihood to respond could prevent someone from having an expensive VNS system implanted while only minimal effects will be obtained.

Most studies that attempt to predict the success of VNS are based upon the localization of the seizure focus, patient characteristics or epilepsy syndrome. However, predictors of success are still elusive. It was found that VNS responsiveness was associated with older age and longer epilepsy duration[5] or rather to be independent of epilepsy duration[6] and associated with younger age.[7] VNS success was found to be related to epilepsy syndromes other than Lennox-Gastaut syndrome[5] or rather to Lennox-Gastaut syndrome[3,8] and tonic seizures.[3] Furthermore, Scherrmann et al.[9] concluded that seizure outcome was positively correlated with VNS duration and Handfort et al.[10] found that seizure reduction was positively correlated with high stimulation settings.

Until now, very few studies evaluated whether success of VNS can be forecasted using the electroencephalogram (EEG).[4,11] There are some more epilepsy surgery studies using EEG as a tool to assess outcome prognosis.[12–14] These studies are all primarily based on the visual analysis of the EEG, for instance by counting the number of Interictal Epileptic Discharges (IED) before onset of the therapy. Janszky et al.[4] showed that absence of bilateral IEDs in the EEG before VNS implantation was associated with a seizure free outcome.

However, observing the different wave-forms in the EEG is subjective and laborious because the results depend on the

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individual neurophysiologists' experience and expertise. Quantitative EEG (qEEG) analysis may partially replace the visual interpretation[15–17] and is a more objective and perhaps sensitive method than visual interpretation of EEG. qEEG may even detect characteristics of the EEG that are not visible for the naked eye, like synchronization measures, power per frequency band and symmetry measures.

We hypothesize that symmetry can be a relevant feature to predict the effect of VNS therapy. Van Putten[18,19] originally proposed the brain symmetry index (BSI) as a measure for electroencephalographic symmetry. The BSI quantifies the spatial EEG symmetry and has found clinical applications for the detection of (focal) ischemia[20,21] and focal seizure activity.[22] We hypothesize that the interictal EEG from patients suffering from (multi-focal) pharmacoresistant epilepsy may be characterized by an increased asymmetry. This is motivated by the observation that in many of these patients, the interictal EEG often shows asymmetric features, e.g. focal slowing or amplitude asymmetries. In this study, therefore, we explore whether baseline EEG symmetry, as quantified by the BSI, is a predictor for success of VNS therapy.

2. Materials and methods

2.1. Patient selection

VNS treated patients were selected retrospectively (see Table 1). All patients suffered from (multi) focal, medically intractable epilepsy with varying focus locations and were scheduled for implantation of a vagus nerve stimulator (Cyberonics, Houston, TX) between 2001 and 2008. All patients were treated at the epilepsy centre SEIN Zwolle. Patients were aged 16 years or older and should have had an EEG recorded shortly before the onset of VNS therapy. During this EEG recording, no epileptic seizure should have occurred, as the interictal EEG pattern is analysed and sufficient minutes of artefact free EEG should be available. Three months prior to implantation and during the first year after implantation anticonvulsant drug intake should have been unchanged.

Patients and their family should have kept seizure diaries for over six months prior to the VNS therapy and during the first one to two years of VNS therapy. The evaluated seizure reduction during therapy was used to determine the success of VNS. The average number of seizures per month was calculated and two definitions were used to define responders. Responders_0 were defined as having any reduction in seizure frequency and responders_{50} had at least 50% seizure reduction.

The stimulation parameters are personalized for each patient. Often the therapy started with a stimulation cycle of 30 s on and 5 min off. The amplitude was increased guided by the effects and side-effects of the stimulation. When further increase of the amplitude was neither effective nor possible, a more rapid stimulation cycle was tested.

2.2. EEG analysis

All EEGs were recorded by trained personnel at the SEIN epilepsy centre. Electrodes were placed according to the 10/20 system, fixed by adhesive and conductive gel. Impedances did not exceed 10 kΩ. Sampling frequency was 200 Hz. Twenty to forty minutes of EEG were recorded, according to standard protocol, containing periods of hyperventilation, eyes closed, eyes open, intermittent photo stimulation and somatosensory stimulation of the hand.

Source reference was used for montage and only periods of closed eyes without any form of stimulation were used for analysis. This was done to avoid qEEG abnormalities due to eye movements or other provocations. Furthermore, periods with IEDs, movement artefacts or periods indicating drowsiness were excluded after visual inspection. At least several minutes of artefact free EEG activity with closed eyes needed to be present for an EEG recording to be analysed. Selected epochs were subsequently filtered with a band pass filter between 0.5 and 30 Hz. Epochs of 400 samples with 50% overlap were Fourier transformed with pwelch in MATLAB (The MathWorks, Inc.) using a Hamming window.

2.3. Features

A new implementation of the BSI was used for analysing brain symmetry. Originally the BSI was proposed as a measure for the mean electroencephalographic spatial symmetry of the brain.[19] More recently, the pdBSI was introduced by Sheorajpanday et al.[21] as a natural extension of the BSI. The pdBSI is a single channel pair wise derived BSI which evaluates asymmetry along homologous channel pairs instead of global asymmetry, which is measured with the BSI. Comparison of homologous channel pairs (pdBSI) instead of global hemispheric differences (BSI) could lead to a more sensitive determination of abnormal asymmetry in epilepsy patients with several or cryptogenic foci. The pdBSI[21] is calculated with:

Table 1
Patient characteristics at onset of vagus nerve stimulation.

No.	Sex	Age (y)	Type epilepsy	Effect VNS (% reduction)	pdBSId baseline	pdBSIt baseline	pdBSIa baseline
1	M	30	Focal	0	0.330	0.304	0.292
2	M	47	Multifocal	50	0.320	0.288	0.303
3	F	56	Focal	60	0.320	0.295	0.281
4	M	16	Multifocal	0	0.312	0.306	0.300
5	M	21	Multifocal	0	0.339	0.327	0.320
6	M	50	Focal	25	0.289	0.287	0.304
7	F	55	Focal	80	0.308	0.286	0.292
8	F	46	Focal	0	0.441	0.435	0.395
9	F	33	Focal	30	0.370	0.342	0.370
10	F	31	Multifocal	0	0.398	0.364	0.325
11	M	41	Focal	60	0.299	0.267	0.271
12	F	63	Focal	0	0.273	0.233	0.243
13	M	42	Focal	0	0.332	0.354	0.326
14	F	39	Focal	50	0.278	0.272	0.281
15	F	47	Focal	50	0.287	0.269	0.259
16	M	64	Focal	80	0.322	0.296	0.302
17	M	45	Focal	25	0.322	0.281	0.335
18	M	29	Focal	0	0.340	0.308	0.306
19	M	16	Focal	0	0.311	0.307	0.315