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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

$$\text{pdBSI} = \frac{1}{N}\sum_{i=1}^{K}\frac{1}{M}\sum_{j=1}^{M}\left|\frac{R_{i,j}-L_{i,j}}{R_{i,j}+L_{i,j}}\right|$$

With $R_{i,j}$ and $L_{i,j}$ the Fourier coefficient belonging to frequency $i = 1, \ldots, K$ of right and left hemispheric bipolar derivations $j = 1, 2, \ldots, M$ for N discrete time points. The bipolar derivations used to calculate the pdBSI are Fp1–Fp2, F3–F4, F7–F8, F9–F10, C3–C4, P3–P4, P7–P8, O1–O2, T7–T8.

The BSI is defined in such a way that the lower the BSI, the higher the EEG symmetry. EEG recordings from "normal healthy brains" result in BSI values of about 0.07[19] and pdBSI values of about 0.13.[21] Increased pdBSI values are obtained if EEG recordings show asymmetries, e.g. focal slowing or differences in amplitudes of homologous channel pairs.

Four different frequency ranges were explored: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). Higher frequency ranges were not investigated because of the low signal to noise ratio for these frequencies when using scalp EEG.

2.4. Statistics

For the discrimination between responders and non-responders based on single features, *t*-tests were applied when data was normally distributed; Mann–Whitney U tests were used when data was not normally distributed. Normality tests were done for all single features using the Shapiro Wilk test. A confidence interval of 95% was used to define significant results. This current study was used to discover promising features that will be tested extensively in our future study.

3. Results

The EEG recordings of only 19 patients matched our inclusion criteria and were analysed. These EEGs were recorded within an interval of six weeks prior to onset of the VNS therapy and contained only few artefacts. The patients included were 11 men and 8 women, with a mean age of 45 years (standard deviation 15 years). 15 patients suffered from focal epilepsy, while 4 had multi focal epilepsy. Due to VNS therapy, 10 patients obtained a reduction in seizure frequency (responders$_0$) of which 7 had a reduced seizure frequency of at least 50% (responders$_{50}$). For all patients, the pdBSI values of all frequency bands were obviously increased compared to the average value of 0.13 for healthy control subjects measured by Sheorajpanday et al.[21] (see Table 1). This indicates that before treatment with VNS, the asymmetry of the EEG activity for all the patients is significantly higher than for healthy controls.

Table 2 shows the *p*-values for the discrimination between responders$_0$ and non-responders$_0$ and between responders$_{50}$ and non-responders$_{50}$ using the pdBSI for the different frequency bands. A lower pdBSI value indicates more symmetry along homologous channel pairs of the two hemispheres. The pdBSI for the theta band (pdBSIt) is significantly lower for responders$_0$ than for non-responders$_0$ and the pdBSI for the delta band (pdBSId) shows a difference between responders$_0$ and non-responders$_0$ as well, however this difference is less convincing. The pdBSI for the alpha band (pdBSIa) is significantly lower for responders$_{50}$ than for non-responders$_{50}$ and both the pdBSId and pdBSIt also show clear differences between responders$_{50}$ and non-responders$_{50}$.

Fig. 1 shows the pdBSI values for responders$_{50}$ and responders$_0$ for the four different frequency bands. Responders have on average lower pdBSI values for all frequency ranges than non-responders, independent of the definition of responders. Relatively low BSI values for responders imply that, prior to the onset of VNS treatment, symmetry in the EEG is yet higher for responders than for non-responders.

Table 2
p-Values for discrimination between responders and non-responders, based on pair wise derived brain symmetry values (pdBSI) for different frequency bands extracted from EEGs recorded before the onset of VNS treatment.

	pdBSI (delta, theta, alpha, beta)			
	pdBSId	pdBSIt	pdBSIa	pdBSIb
Non-responders$_0$ vs. responders$_0$	0.09	0.01*	0.31	0.94
Non-responders$_{50}$ vs. responders$_{50}$	0.07	0.06	0.02*	0.14

* p-Value < 0.05.

Results show that responders$_{50}$ have slightly lower BSI values than responders$_0$. In addition, the variance in the pdBSI of the non-responders is in general much larger than the variance in the pdBSI of the responders. Differences between responders$_{50}$ and non-responders$_{50}$ are larger than between responders$_0$ and non-responders$_0$.

4. Discussion

In this study, we evaluate particular symmetry measures of the EEG in their ability to predict whether patients will respond with a seizure reduction to vagus nerve stimulation. It is found that local symmetry values (pdBSI), especially for the delta, theta and alpha frequency ranges, correlate with a positive response to VNS treatment. Although in patients the pdBSI values are higher than in healthy controls, non-responders have significantly higher pdBSI values before the onset of VNS treatment than responders.

In many patients suffering from epilepsy, in particular focal seizures, the interictal EEG may show local abnormalities, e.g. focal

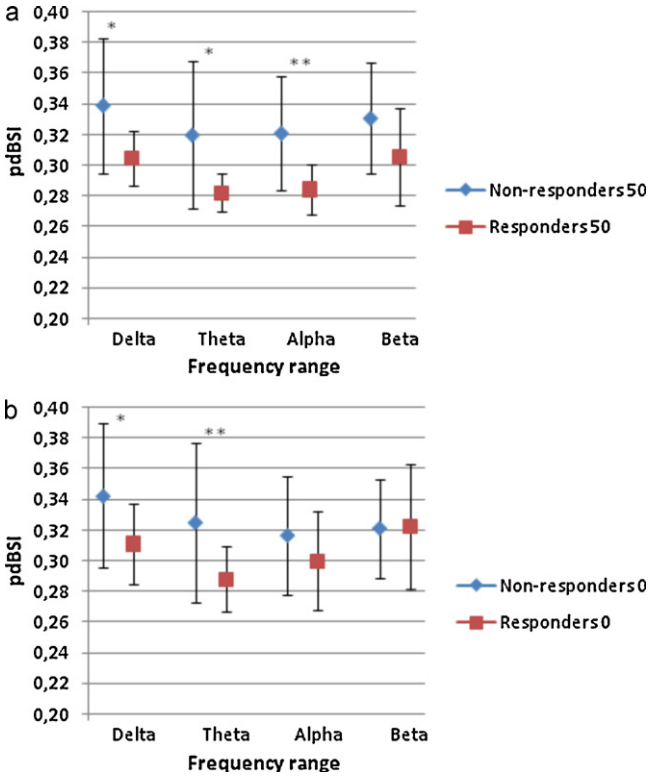

Fig. 1. Differences between (a) responders$_{50}$ ($n = 7$) and non-responders$_{50}$ ($n = 12$) and (b) responders$_0$ ($n = 10$) and non-responders$_0$ ($n = 9$) in pdBSI for the delta, theta, alpha and beta band, extracted from EEGs recorded before onset of VNS treatment. Error bars represent the standard deviation. $^*p < 0.1$, $^{**}p < 0.05$.

slowing or differences in amplitude, which will increase the pdBSI values. In this study, we indeed found that for all patients the pdBSI values are higher than for healthy controls. In addition, non-responders showed significantly higher pdBSI values than responders. This suggests that in patients with only mildly abnormal EEGs, as reflected by the moderate increases in the pdBSI, VNS is more likely to have a clinically relevant effect. As the amount of asymmetry as quantified by the pdBSI, may indeed reflect the deviation from normal, VNS seems relatively more effective in mild cases.

It was also found that, using the BSI to quantify hemispheric symmetry, we can better predict whether a patient will have a seizure reduction of more than 50% ($responder_{50}$), than that we can predict any seizure reduction at all ($responder_0$). Patients who have experienced a seizure reduction of less than 50% were patients with limited response to the therapy. Including these poor-responders in a statistical analysis decreases the power. Although our study population is too small to differentiate between more gradual responses, it appears that brain symmetry values are most suited to identify the best responders.

Anticonvulsant drugs may influence several characteristics of the EEG. The patients in this study all used combinations of two to four different anticonvulsant drugs. Many patients used combinations including valproic acid, carbamazepine or lamotrigine. However, the effects of anticonvulsants on the EEG are typically minor and global rather than focal, e.g. a minimal reduction in alpha mean frequency.[23] Therefore, the effect of anticonvulsants on the BSI will be minimal, if present at all. Indeed, a correlation between pdBSI values and particular anticonvulsant drugs was not found.

Evaluation of the interictal EEG to predict success of vagus nerve simulation was previously briefly described by Majoie et al.[11] who mentioned a lower average background frequency and more interictal epileptiform abnormalities in patients who did not respond to VNS treatment. The obtained difference in background frequency in their study was however not statistically significant. Research done by Janszky et al.[4] showed that the absence of bilateral IEDs predicted success of VNS treatment. Quantification of the EEG patterns in both previous studies was difficult, as the authors used primarily visual inspection of the EEG recordings, whereas our approach is also feasible when there are no IEDs visible and allows more objective quantification of predictive EEG characteristics.

Various related studies used qEEG features to evaluate VNS therapy, rather than to predict its effects.[24–26] In these studies of the interictal EEG, low EEG frequencies (i.e. delta–theta–alpha) have been found to be most relevant, and associated with various epilepsy syndromes. Novak et al.[26] found that the chronic effect of VNS on the interictal EEG showed a trend towards decreased delta power and increased alpha power. Marrosu et al.[25] investigated background interictal EEG in awake epilepsy patients after therapy as well. They evaluated both changes in the power spectrum and the synchronization level using the cross spectral density function normalized by individual auto-spectral density functions.[27] In eleven subjects, the intra- and inter-hemispheric synchronization in the theta band (4–7.5 Hz) both decreased, whereas the power of the gamma band (20–50 Hz) and the intra-hemispheric synchronization increased. Since evaluation of qEEG changes is very relevant and may provide important information about potential mechanisms of VNS therapy, we have also studied qEEG changes due to VNS therapy. However, this is beyond the scope of this paper. We have chosen to focus on prediction, as predicting the response to VNS will provide great clinical benefits. Determining features that will predict potential responders and provide patients with information about the expected seizure reduction will increase the efficacy of VNS therapy.

This study is a first exploration of predictive qEEG features to identify responders to VNS therapy. Although we were not able to predict the effect of VNS for the individual patient, EEG symmetry quantified by pdBSI seems a relevant feature. Additional validation of the proposed BSI features and the creation of a prediction model are subjects of our future study.

5. Conclusion

In sum, our study shows that EEG symmetry features may be useful to predict the success of VNS therapy. Brain symmetry index values in the different frequency bands show that patients who will not respond to VNS treatment have, on average, more asymmetric spectral characteristics of the interictal EEG than responders.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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