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

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ABSTRACT

Purpose: Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy, with achieving more than 50% seizure reduction in one third of the treated patients. In order to predict which patients will profit from VNS, we previously found that a low pairwise derived Brain Symmetry Index (pdBSI) could potentially predict good responders to VNS treatment. These findings however have to be validated before they can be generalized.
Methods: 39 patients (age 18–68 years) with medically intractable epilepsy who were referred for an implanted VNS system were included. Routine EEG registrations, recorded before implantation, were analyzed. Artefact-free epochs with eyes open and eyes closed were quantitatively analyzed. The pdBSI was tested for relation with VNS outcome one year after surgery.
Results: Twenty-three patients (59%) obtained a reduction in seizure frequency, of whom ten (26%) had a reduction of at least 50% (good responders) and thirteen (33%) a reduction of less than 50% (moderate responders). Sixteen patients without seizure reduction are defined as non-responders. No significant differences were found in the pdBSI of good responders (mean 0.27), moderate responders (mean 0.26) and non-responders (mean 0.25) ($p > 0.05$). Besides seizure reduction, many patients (56%) reported additional positive effects of VNS in terms of seizure duration, seizure intensity and/or postictal recovery.
Conclusion: EEG features that correlate with VNS therapy outcome may enable better patient selection and prevent unnecessary VNS surgery. Contrary to earlier findings, this validation study suggests that pdBSI might not be helpful to predict VNS therapy outcome.

1. Introduction

Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy in numerous patients. However, long-term studies showed that a good response (>50% seizure reduction) is only achieved in 20–55% of the patients [1–3], which means that a substantial number of patients only show moderate or even no response to VNS treatment. 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 undergoing surgery and having an expensive VNS system implanted while only minimal effects will be obtained. Despite the growing application of VNS, it is still not possible to predict which patients respond to what extent to VNS therapy. Most studies that attempt to predict the success of VNS are based upon patient characteristics [4], epilepsy syndrome [5] or localization of the seizure focus [2,6,7]. A meta-analysis by Englot et al. on predictors of response to VNS therapy, showed that young patients (<6 years) respond slightly better in terms of seizure reduction compared to adults [2]. However, good predictors of efficacy of VNS therapy for individual patients are still elusive.

We previously showed that quantifying EEG asymmetry using the pairwise derived Brain Symmetry Index (pdBSI) could potentially predict which patients will benefit from VNS treatment. It was observed that non-responders show significantly higher EEG

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asymmetry, reflected in higher pdBSI values, as compared with responders [9]. These findings however require validation in new patient groups before they can be generalized. We have therefore conducted this prospective study in adult epilepsy patients without cognitive impairment; expecting to confirm the predictive value of EEG symmetry, as defined by pdBSI.

2. Materials/methods

2.1. Patients

We have included otherwise healthy epilepsy patients (age > 18 years) who were referred by SEIN Centre of Excellence for Epilepsy and Sleep Medicine (Epilepsy Centre) to Medisch Spectrum Twente hospital for implantation of a VNS system. All patients suffered from medically intractable (generalized or localized) epilepsy with varying focus locations. Patients had to keep seizure diaries for at least six months prior to implantation and during the one year follow up period of the study.

2.2. VNS outcome

After implantation, patients have regular follow up visits at their Epilepsy Centre. During these visits, stimulation parameters are optimized for the individual patient and the effect of VNS therapy is monitored. The success of VNS was determined by the amount of seizure reduction due to the therapy. Patients were grouped as good (>50% reduction), moderate (<50% reduction) and non-responders (no reduction) based on seizure diary data provided by the treating nurse practitioner from the Epilepsy Centre.

In addition, patients are asked to fill in a questionnaire about the effects of VNS and their satisfaction with the device approximately one year after implantation. The questionnaire addresses various parameters such as seizure frequency, duration and intensity, postictal recovery, patient satisfaction, and side-effects. Patients indicate how much various parameters have improved or worsened upon VNS therapy on a 7-point scale (Clinical Global Impression – Improvement scale, CGI-I), where 1 means very much improved and 7 means very much worsened. Data from questionnaires was used to compare patient's own perception with the data from the Epilepsy Centre and is used to make a second classification, where CGI-I scores 1–2 = good responder, score 3 = moderate responder, scores 4–7 = non-responder.

2.3. EEG analysis

Thirty-minute routine EEG registrations were made several weeks before VNS implantation. Electrodes were placed conform the international 10–20 system, using an electrocap and signal was recorded using a BrainLab EEG recording system (OSG BVBA, Belgium) with a sampling frequency of 250 Hz. During the registration, the patients were comfortably lying down in a quiet, shielded room. Artefact-free epochs with eyes open and eyes closed were selected for quantitative analysis. Selected epochs were filtered with a bandpass filter between 0.5 and 30 Hz. Epochs of 500 samples with 50% overlap were Fourier transformed with pwelch in MATLAB (The Mathworks, Inc., USA) using a Hamming window.

Brain symmetry was quantified using the pair-wise derived Brain Symmetry Index (pdBSI), which was described previously [9–11]. Briefly, the pdBSI evaluates asymmetry by calculating the power per frequency coefficient along homologous EEG channel pairs. Low pdBSI values represent symmetric EEG activity, whereas higher pdBSI values indicate higher asymmetry of the EEG. For each patient, pdBSI values were determined for four different frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). EEG symmetry, defined by pdBSI, was tested for relation with effect of VNS therapy after one year.

2.4. Statistics

Statistical analyses were performed using *t*-tests when (normal distribution) and Mann–Whitney *U* tests (non-normal distribution) with a confidence interval of 95%.

3. Results

3.1. Patient characteristics

Between March 2011 and January 2015, 39 patients had a routine EEG recorded a few weeks prior to implantation of a VNS system and gave informed consent to analyze EEG characteristics and look for relation with VNS effects. Patient characteristics are summarized in Table 1. Patients were not considered surgical candidates and their intellectual ability varied, however none of the patients was severely cognitively impaired. For all 39 patients, data provided by the nurse practitioner (follow-up time on average 14 months, range 8–24 months) and pdBSI values are available. Five out of 39 patients did not send back the questionnaire about their perception of effects and satisfaction with the VNS therapy so this information is only available for 34 patients (follow-up time on average 14 months, range 6–36 months).

3.2. Effects of VNS

3.2.1. Seizure reduction

Based on data provided by the nurse practitioner, twenty-three patients obtained a reduction in seizure frequency, of whom ten had a reduction of at least 50% (good responders) and thirteen a reduction of less than 50% (moderate responders). The other sixteen patients did not show any reduction in seizure frequency and were defined as non-responders to VNS therapy. Neither the patient's age nor the type of epilepsy correlated with the seizure reduction obtained with VNS and therefore these parameters could not predict the effect of VNS (Table 1).

Besides seizure reduction, other positive effects of VNS treatment were reported by the nurse practitioner. Out of sixteen patients who were defined as non-responders, seven patients still experienced other positive effects of VNS. Also, the majority of the good responders (7 out of 10) and moderate responders (8 out of 13) showed additional positive effects in terms of seizure duration, seizure intensity and/or postictal recovery.

3.2.2. Patient perception

In addition to the data provided by the nurse practitioner, VNS outcome was determined using patient questionnaires. Ten patients indicated that their seizure frequency has improved very much or much (CGI-I score 1 or 2). Fourteen patients mentioned a small improvement in seizure frequency (score 3) and ten patients indicated that the seizure frequency had not changed (score 4). No patient indicated worsening of seizure frequency. The patient's general impression regarding seizure frequency only partly corresponded with the percentages of seizure reduction that were provided by the nurse practitioner (Table 1).

All patients who indicated that their seizure frequency has (very) much improved also experienced (some) improvement in seizure intensity and/or postictal recovery. Majority of the fourteen patients who reported minimal improvement in seizure frequency also report little or no improvement in seizure intensity and

Table 1
Patient characteristics and effect of VNS. Effect of VNS reduction is based on the data from seizure diaries provided by the treating nurse practitioner. Patient's perception of seizure reduction and patient's overall satisfaction with the VNS device are based on the Clinical Global Impression – Improvement (CGI-I) scores. (NA: information is not available).

No.	Sex	Age (years)	Focus location	Effect VNS (% reduction)	Patient perception of reduction	Patient overall satisfaction
1	M	68	Multi focal	>50	1	1
2	F	37	Multi focal	>50	2	1
3	F	27	R temporal	>50	1	1
4	M	45	Multi focal	>50	4	4
5	F	46	Multi focal	>50	3	2
6	F	40	R temporal	>50	3	3
7	M	19	Multi focal	>50	2	3
8	F	23	Multi focal	>50	3	4
9	F	27	L temporal	>50	2	2
10	M	62	R temporal	>50	NA	NA
11	F	31	Frontal	<50	2	4
12	M	21	R temporal	<50	2	3
13	F	54	Multi focal	<50	4	6
14	F	25	Multi focal	<50	3	3
15	F	49	R temporal	<50	4	3
16	M	60	L temporal	<50	3	3
17	F	35	R temporal	<50	3	3
18	M	65	Multi focal	<50	4	4
19	F	59	Multi focal	<50	2	2
20	F	54	R temporal	<50	3	2
21	F	22	L temporal	<50	3	2
22	F	26	Multi focal	<50	NA	NA
23	F	20	Multi focal	<50	NA	NA
24	F	51	L temporal	0	3	3
25	F	48	R temporal	0	4	7
26	F	52	Multi focal	0	2	3
27	M	51	Multi focal	0	2	3
28	M	47	Multi focal	0	3	4
29	F	42	Frontal	0	4	6
30	F	18	Multi focal	0	3	3
31	M	31	Multi focal	0	4	6
32	M	20	Frontal	0	4	NA
33	F	19	Multi focal	0	3	5
34	M	62	Multi focal	0	3	3
35	F	24	Multi focal	0	3	4
36	M	32	Frontal	0	4	5
37	M	35	Multi focal	0	4	3
38	F	28	Multi focal	0	NA	NA
39	M	46	Multi focal	0	NA	NA

recovery after seizures. However, three of these patients mentioned much improvement in intensity, recovery, or both. The non-responders, reported little or no improvement in terms of seizure intensity and postictal recovery.

To assess their overall satisfaction with the VNS therapy, patients were asked how satisfied they were on a scale of 1 (very satisfied) to 7 (very dissatisfied). This time the whole scale was used by the patients and on average they scored 3.4. As expected, the extent of satisfaction is strongly correlated with the effects of the stimulator. In the good responder group (according to the nurse practitioner) the average satisfaction is 2.1, whereas the moderate and non-responders score 3.2 and 4.2, respectively.

3.2.3. Side effects

Most patients (33 out of 39) experience side-effects from VNS treatment, independently of the effectiveness of VNS (Table 2). Some patients experience more than one type of side-effect. Side-effects that were mentioned occur only during stimulation. In general, comparable occurrence and type of side effects are experienced by all three groups.

Table 2
Reported side effects. Numbers indicate number of patients per group (good, moderate, non-responder) reporting the respective side-effect. Some patients experience multiple types of side-effects.

Side effect	Good resp. (#8/10)	Moderate resp. (#12/13)	Non-resp. (#13/16)	Total (#33/39)	
Hoarseness	7	8	8	23	70%
Throat discomfort	3	2	6	11	33%
Voice alterations	2	5	1	8	24%
Shortness of breath (during exercise)	1	2	3	6	18%
Tingling sensation in neck/shoulder/arm	2	0	1	3	9%
Painful jaw/teeth	0	0	2	2	6%
Coughing	0	1	0	1	3%
Snoring	1	0	0	1	3%

3.3. Pairwise derived Brain Symmetry Index (pdBSI)

3.3.1. EEG

Artefact-free EEG signal of interictal episodes was used to determine the pdBSI. Epochs of 10 s with eyes open and eyes closed were selected. For each patient – for eyes open on average 54 s and for eyes closed on average 57 s of – EEG signal was available for quantitative analysis. No statistically significant differences were observed between pdBSI values obtained from EEG periods with eyes open and eyes closed (Fig. 1).

3.3.2. Relation pdBSI and seizure reduction

Patients were grouped as good, moderate and non-responders based on seizure reduction as indicated by the nurse practitioner. No significant differences were observed between pdBSI values in delta, theta, alpha and beta bands, for good responders compared with moderate responders and non-responders (Fig. 1A). Additionally, patients were classified based on their own reported seizure reduction. Even though this is a partially different grouping, it results in only slightly different average pdBSI values for all frequency bands and again no significant differences were observed (Fig. 1B). Similarly, patients classified based on their own overall satisfaction with VNS, does also not show any significant differences in pdBSI values between good, moderate and non-responders (Fig. 1C).

4. Discussion

To prevent patients who will not respond to VNS treatment from undergoing unnecessary surgery, it is necessary to find predictors of the expected success of VNS. Low pdBSI values showed promising results in predicting good responders to VNS treatment in a previous study [9]. However, we have not been able to reproduce the previous findings in this current study. Although

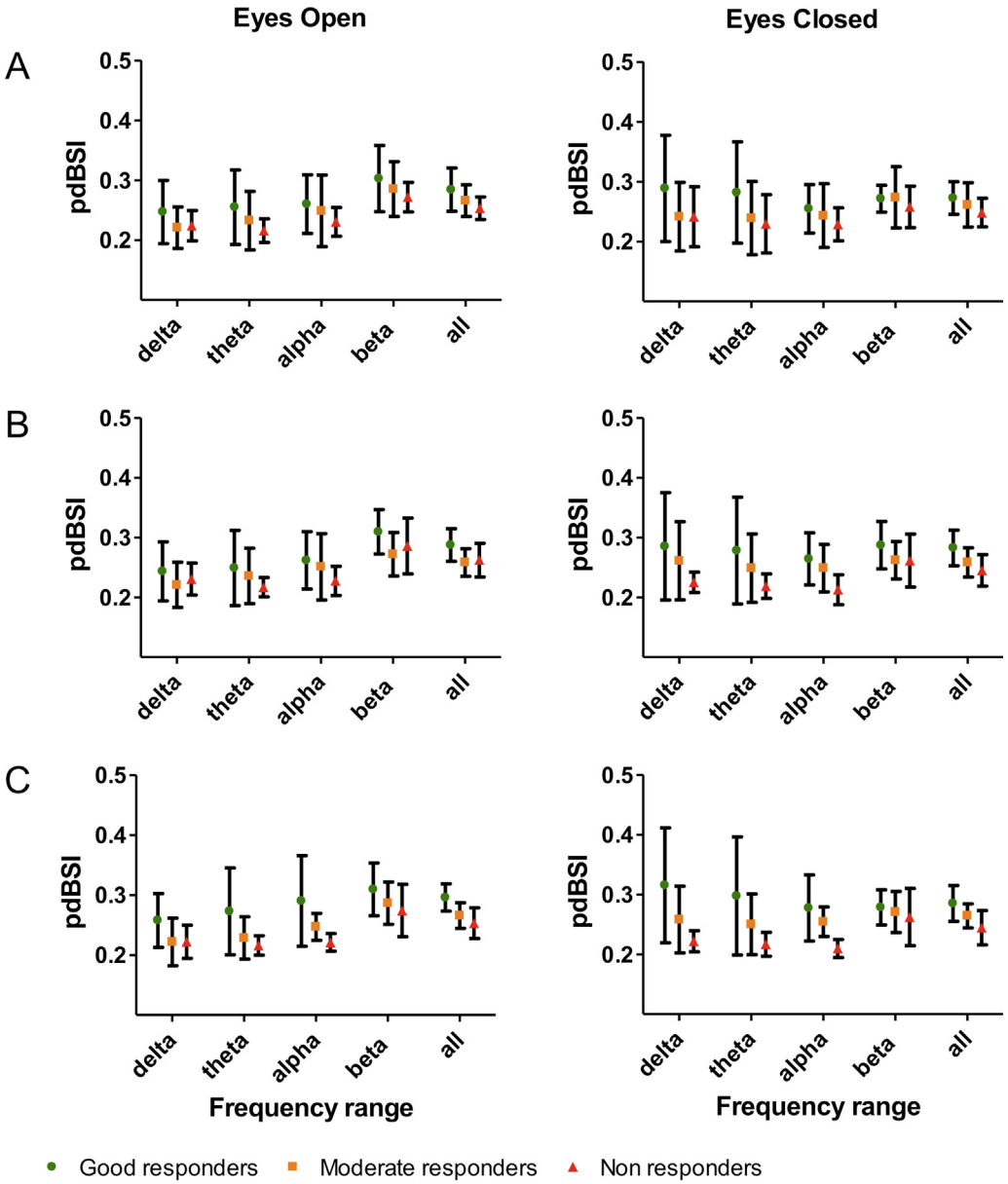

Fig. 1. Differences between good responders, moderate responders, and non-responders in pdBSI for the delta, theta, alpha and beta band and averaged over all frequencies, for EEG periods with eyes open and eyes closed. Classification good, moderate and non-responders was based on: (A) data provided by the treating nurse practitioner, (B) patient's perception of seizure reduction, and (C) patient's overall satisfaction with the therapy. Error bars represent the standard deviation.

the study population of this current study was larger than in our previous study ($n = 39$ versus $n = 19$), the number of patients is still relatively small, and again the study population consists of a heterogeneous group of patients that are not suitable or willing to undergo epilepsy surgery. Previously we based our analyses only on the information provided by nurse practitioners, whereas in this study we also included two measures of the patients' own perception of VNS outcome, and evaluated pdBSI values of EEG recording with eyes open as well as with eyes closed. Nevertheless, no significant differences in pdBSI values were observed within these various conditions or outcome measures.

This prospective study enabled a long-term follow-up of the same patient population, eliminating the influence of potential early dropouts that may be missed in retrospective studies. In our study, most patients experience moderate (33%) to good (26%) seizure reduction upon VNS therapy. Studies in younger patients have shown a better response to VNS therapy [2,7,8]. However, our study included only adults. Even though only 26% of the patients had strong seizure reduction upon VNS treatment (data provided by nurse practitioner), most patients (62%) indicated that they were in general (somewhat to very) satisfied with the device. This may be related to other positive effects many patients experience besides seizure reduction, such as reduced seizure intensity or duration and/or shorter postictal recovery times, also of importance to the patient. In addition, potential reduction of nocturnal seizures, which may not be noticed and thus not reflected in reduced seizure frequency, may result in an improved sleep quality, increased daytime alertness and a better overall health condition [12]. On the other hand, patients who show seizure reduction upon VNS treatment may experience negative side-effects that could influence their perception of seizure reduction and decrease their overall satisfaction with the therapy. In our study, nearly all patients (85%) experienced some, mostly mild, side-effects. This percentage is higher than described by others, however, the type of reported side-effects is similar [13,14].

Patients were defined as either good, moderate or non-responders based on the amount of their seizure reduction as provided by nurse practitioners, based on seizure diaries kept by the patients themselves, which is still the standard, but has nevertheless limited accuracy [15]. Hence, the discrepancy with the patients' own perception of seizure reduction as well as their satisfaction with the therapy, when asked one year after implantation. We found that seizure reduction as experienced by patients (CGI-I scale) differed substantially from the seizure reduction provided by the nurse practitioner. Patients' own perception could be both better or worse than what the nurse practitioners' data suggested and 18 patients were classified differently. Possibly, this classification is influenced by other factors like side-effects or general satisfaction with the therapy, even though we have tried to prevent this by asking about these aspects in separate questions. Nevertheless, patients' perception of seizure reduction is asked only once after one year as a score on a 7-point scale, which is a different measure than the information based on daily seizure diaries. Moreover, interpretation of the 7-point scale may vary amongst patients. One patient may score a 30% seizure reduction as 'very much improved' whereas another patient may score the same percentage of seizure reduction as 'minimally improved', probably coloured by the impact that (various types of) seizures have on the patient's daily life.

In contrast to our earlier findings, the current data indicate that EEG symmetry quantified as pdBSI values might not correlate with patient satisfaction or with seizure reduction due to VNS therapy and can therefore not be used as a predictor of the effect of VNS. New studies need and will be conducted to continue the search for biomarkers to reliably predict the effects of VNS therapy and enable better patient selection and prevent unnecessary surgical procedures.

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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.

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