

Priming the Epileptic brain (PREP)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AED	Anti-epileptic drug
AR	Adverse Reaction
BRV	Brivaracetam
BS	Brain Stimulation
CE	Conformité Européenne
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
DTI	Diffuse Tensor Imaging
EEG	Electroencephalography
EudraCT	European drug regulatory affairs Clinical Trials
fMRI	Functional Magnetic Resonance Imaging
GMP	Good Manufacturing Practice
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SD	Standard deviation
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SV2A	Synaptic Vesicle glycoprotein 2A
SUSAR	Suspected Unexpected Serious Adverse Reaction
tDCS	Transcranial Direct-Current Stimulation
T1	Telephone call 1
TMS	Transcranial Magnetic Stimulation (TMS)
tVNS	Transcutaneous Vagal Nerve Stimulation
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)
V1	Visit 1

VNS Vagal Nerve Stimulation

QL-VAS

SUMMARY

Rationale: The most prevalent neurological disorder with also immense burden of disease, epilepsy, is in over 30 percent of patients difficult to treat. The ideal treatment regime would give complete control of disease in an early stage, not only for patient well-being, but also to prevent the onset of persistent pathologic epileptic networks in the brain. The first step in treatment is the trial, and error, of multiple anti-epileptic drugs (AEDs), while invasive brain stimulation (BS) techniques with network modulating properties are saved as a last resort. We hypothesize that pharmacotherapeutical treatment of epilepsy can be more successful after “priming” (preparing) the brain using BS as a short-term neuromodulation treatment. The limitation of testing this hypothesis is the invasive aspect of the most used classic vagal nerve stimulation (VNS) treatment for epilepsy, but the recent development of transcutaneous vagal nerve stimulation (tVNS) offered a possibility to combine chemical and electrical modulation in an earlier stage of disease, which is not tested before.

Objective: Determine the priming effect on the epileptic brain of transcutaneous vagal nerve stimulation (tVNS), to make it more susceptible to add-on treatment with Brivaracetam (BRV), an anti-epileptic drug (AED). In addition, we aim to visualize these changes in the brain because of priming, possibly altered network-organisation.

Study design: Randomized Controlled Trial.

Study population: Adult patients (18-65 years) with a refractory (continuing of seizures despite 2 tried AEDs) focal epilepsy of unknown etiology and therefore have an indication for start of brivaracetam.

Intervention: One group receives transcutaneous vagal nerve stimulation (tVNS) 4 hours daily for the first 3 months of brivaracetam treatment.

Main study parameters/endpoints: scoring on a compensatory index combining seizure reduction, improvement of cognition and quality of life.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Besides minor side effects no risk is attributed to tVNS. Because of the study one extra visit is necessary, besides regular clinical follow-up. The 3 visits do require some more time than usual because of the questionnaires, MRI and short cognitive tests.

1. INTRODUCTION AND RATIONALE

Epilepsy is the most prevalent neurological disorder in the Netherlands, affecting roughly 120.000 individuals. The impact of the disorder is considerable for patients, especially if the epilepsy is refractory to treatment. The condition pharmacoresistant or refractory epilepsy is met when complete control is not achieved after the use of two anti-epileptic drugs (AEDs), which is the case in approximately 30 percent of patients. In current practice, the next step is treatment with a newer AED, for example BRV which is registered as add-on treatment for focal epilepsy in adults. Nevertheless, the development of novel AEDs in recent decades has not resulted in an improvement of the total amount of patients who become seizure free. Alternatively, epilepsy surgery and brain stimulation (BS) can be used in this group of patients. These treatments are however **last-resort** tools because of their invasive character. A new treatment regime that controls disease in an earlier stage is desperately needed.

In recent years, the insight into the neuronal mechanisms of epilepsy has changed towards a paradigm in which pathologic brain networks are considered important. Accordingly, a powerful modifier of these pathological networks might be the key in successful epilepsy treatment. For BS it is known that there is a mode of action through network modulation, as specific and long lasting cerebral plasticity have been described after stimulation in recent animal and human studies, including Vagus Nerve Stimulation (VNS) [Hays 2013]. In addition, even in diseased brain effectiveness of VNS-based targeted plasticity therapies has been demonstrated, for example when paired with rehabilitation therapy [Hays 2015]. Given these results, BS might alter pathological epileptogenic networks beneficially as well, what could be a more plausible and constructive approach than pharmacological suppression of seizures.

As mentioned before, BS also gained status as a so-called priming tool in the treatment of various brain diseases [Rumi 2005, Perez 2014, Hays 2015]. Priming can be described as augmenting the sensitivity of the brain to therapy by applying techniques that change the excitability of the cortex. Diverse non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS), transcranial direct-current stimulation (tDCS) and VNS have been used to prime the brain in order to maximalize the effects of further therapy, such as motor rehabilitation therapy in stroke or chemical treatment in depression [referentie]. Even though the exact mechanisms of BS priming remain unknown, there is evidence suggesting that priming facilitates network modulation [Hays 2015]. Notably, these effects persisted after discontinuation of therapy.

All data considered, there are reasons to believe that there is a role for the use of BS at an earlier stage in the treatment of epilepsy. One might hypothesise that by directing neural plasticity in pathological epileptic networks using VNS techniques, the epileptic brain can possibly be “primed” (prepared) for consecutive AED treatment. The limitation of testing this hypothesis is the invasive aspect of classic VNS treatment and most other BS techniques. The stimulation electrode is irreversibly attached at the stimulation site, and the implanted device has a battery which requires frequent replacement [Klooster 2016]. Recent development of a non-invasive vagus nerve stimulation technique offers possibilities. Transcutaneous auricular VNS (tVNS) applies stimulation via the auricular branch of the vagal nerve in the concha of the ear. In a recent randomized clinical trial, the beneficial effects of tVNS in drug resistant epilepsy were described [Bauer 2016]. However, the included patients already had a long history of epilepsy (average of 23.6 years), while we hypothesize that tVNS more early in the disease course might be more effective. For example, because of the experience in clinical practice that persistent epilepsy is increasingly more difficult to treat. Moreover, Bauer et al left the AED treatment regimen unchanged, while we hypothesize that the combination of tVNS and a new AED could work synergistic. Last but not least, if the priming theory also goes for epilepsy treatment, it encompasses a temporary intervention instead of the current chronic use of VNS.

To determine whether an epileptic brain has been primed or not, suitable measures needs to be defined. Besides clinical parameters, functional MRI (fMRI) also provides a non-invasive window into brain activity. In addition to traditional task-based fMRI, resting-state fMRI (RS-fMRI) allows for visualizing baseline activity of the human brain by focusing on spontaneous fluctuations in the BOLD (blood oxygen level-dependent) signal. These fluctuations in brain activity form highly correlated patterns, so-called resting state networks (RSNs), which, in principle, reflect the full functional repertoire of the brain. A popular approach to spatially identify these RSNs is based on a mathematical technique called independent component analysis (ICA) [Lee 2013]. In patients with epilepsy, connectivity abnormalities have been found in RSNs such as the epileptogenic, cognitive and sensory processing networks [Centeno 2014]. In this way, fMRI can be used to identify changes in these RSNs as a result of treatment, that might be a read-out of successful therapy and possibly give more insight in the exact working mechanism of tVNS and priming.

To conclude, the availability of tVNS as an unobtrusive method of VNS makes combining chemical and electrical modulation techniques more obvious and more feasible, especially in the earlier course of disease. In this study we propose a protocol in which the

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epileptic brain is shortly treated by electrical modulation using tVNS, in order to prime the epileptic brain for chemical treatment using Brivaracetam.

2. OBJECTIVES

The main objectives are:

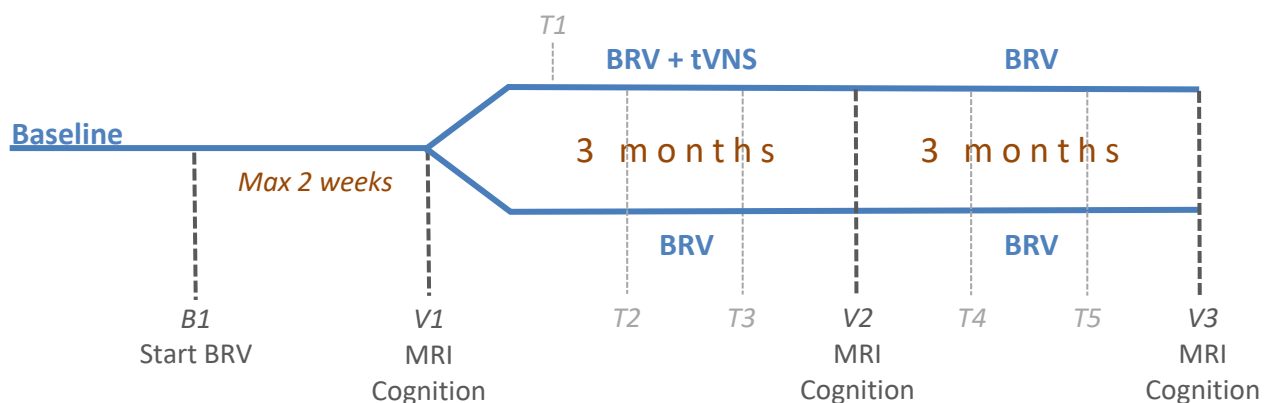
- a) To determine the effect of tVNS as an electrical neuromodulation technique on priming the epileptic brain for add-on AED treatment with Brivaracetam.
- b) To determine differences in network-organization between patients ‘primed’ with short-term tVNS versus patients who have not been ‘primed’.

Hypothesis: We hypothesize that pharmacotherapeutical treatment of refractory epilepsy can be more successful after “priming” the brain using tVNS as a temporary neuromodulation treatment. Furthermore, we expect that successful priming can be visualised by changes in network-organization.

3. STUDY DESIGN

We will use a cohort of 60 patients with refractory focal onset epilepsy of unknown etiology, that starts add-on treatment with a new generation AED, Brivaracetam (BRV). They will be randomised in a study comparing i) 6 months of pharmacological treatment, of which the first 3 months combined with tVNS (intervention group), versus ii) 6 months of pharmacological treatment with BRV alone (control group). In each group a total of 30 patients will be included. A placebo controlled study is not possible because of the lack of a true sham stimulation. Because of ethical considerations, an interim analysis will be performed at inclusion of 20 patients in each group to determine if there is a statistically significant difference in outcome measures. Besides the clinical endpoints like quality of life and seizure frequency, additional cognitive tests and MRI scanning will be performed at baseline, 3 months and 6 months, to assess the effect and working mechanism of tVNS and its durability.

Figure 1 Patient inclusion (n=60)



4. STUDY POPULATION

4.1 Population (base)

Adult patients with a refractory focal epilepsy of unknown etiology will be included in the study. Patients will be recruited from the outpatient clinic of the Academic centre for Epileptology Kempenhaeghe/MUMC+ and the outpatient clinic of the department of Neurology of the Elizabeth-TweeSteden Hospital in Tilburg (optioneel).

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- EEG confirmed focal epilepsy of unknown etiology which is refractory (at least 2 different AEDs tried) and therefore has an indication for start of brivaracetam
- Subjects with 2 or more seizures per month
- Age >65 years
- IQ > 70 as measured with the Raven's Progressive Matrices

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Randomisation not possible within 2 weeks after start of brivaracetam
- History of another cerebral disorder (neurodegenerative diseases, tumours)
- Inability to provide informed consent
- Any contra-indication for brivaracetam
- Current use of levetiracetam (because of phasing out when starting brivaracetam)
- Current treatment with neurostimulation
- Inability to handle the tVNS device personally
- Subjects that have a current diagnosis of cardiac arrhythmic disease
- Inability to complete cognitive tests
- Any contraindication for MRI: metallic foreign body, pacemaker, claustrophobia, pregnancy

4.4 Sample size calculation

Based on a previous studies with both tVNS and with BRV a power calculation ($\Delta=0.0002$, $SD=0.00023$) is performed with MadCalc software aiming to distinguish an improvement on the composite index of $> 2/3^{\text{rd}}$ sd (seizure reduction, cognitive improvement, improvement of QOL), as this is a difference which is considered to have a potentially clinical relevance (Cohen, 1977.). The power calculation showed that a sample size of 18 per group is required to reach a statistical power of 80% (i.e. $\beta=20\%$ risk of type II errors) at $\alpha=0.05$ (i.e. 5% risk of type I errors). Furthermore, a subject drop-out of 10% is estimated. Finally as the study uses two treatment arms, a gain of power of 30% is estimated. Therefore, in total 40 subjects are needed.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients in the intervention group will be additionally treated with tVNS for the first 3 months of BRV treatment.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication

Therapy intended for the acute treatment of seizures can be used as normal, such as benzodiazepines. This also applies to the treatment of a status epilepticus where current guidelines are leading.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The intervention group will receive 3 months of treatment with transcutaneous vagal nerve stimulation (tVNS). Vagal Nerve Stimulation (VNS) is the most used neurostimulation technique for the treatment of refractory epilepsy and has been used for more than 20 years. This traditional VNS method uses an implantable device with an electrode wrapped around the vagus nerve in the neck. Transcutaneous vagus nerve stimulation (tVNS) can stimulate the auricular branch of the vagus nerve through the skin of the outer ear. The study will use the CE certificated t-VNS device NEMOS® (Cerbomed GmbH, Erlangen,

Germany), and the intended study population is within the CE approved indication for use. The system includes an external pulse generator, roughly the size and weight of a cellular telephone, with a cutaneous contact electrode that is placed in the auricular tract. Placement of the electrode is designed to be a simple process, and patients are instructed on proper technique prior to using the device. A rechargeable Lithium battery powers the pulse generator, and the electrode is connected to the pulse generator via a connector cable. The rechargeable battery, battery charging station, and connector cables are included with the device. The used device settings are described in table 1. The technical support will be provided by the department of electrical engineering at TU Eindhoven. All personnel involved with the device will be appropriately trained in the requirements specific to this product.

Figure 2: t-VNS device NEMOS ® with extern stimulator, placed in the auricular tract.



Table 1: tVNS device parameters

Pulse duration	200-300 μ s
Duty cycle	30 seconds on, 30 seconds off
Current	Set just below the threshold for painful stimulation (subject dependent)
On / 24 hours	4 hours (subject dependent which hours)

6.2 Summary of findings from non-clinical studies

Animal studies showed no significant difference between VNS and tVNS for treatment of pentylenetrazole induced epilepsy rats [He 2009, He 2013]. In both treatment groups seizure activity measured with epidural EEG traces was significantly reduced, moreover the effects outlasted the period of stimulation.

6.3 Summary of findings from clinical studies

Preliminary studies show that tVNS has the same effect as the implanted VNS device with the advantage that the therapy can be easily stopped when in-effective. The evidence that

supports the use of tVNS was initiated by a small pilot study by Stefan et al [Stefan 2012]. Rong et al found a significant seizure reduction of 42.6 versus 11.5% in the control group in a randomized controlled trial in 144 patients [Rong 2014]. They also found a significant improvement in quality of daily life. Another recent randomized controlled trial by Bauer et al. in 70 patients showed a seizure reduction of 23 percent in the treatment group compared to -2.9 percent in the active control group, which was however not statistically significant. Side effects of tVNS include dizziness, headache and local pain, dysaesthesia and itching at the stimulation site. All the side effects were reversible and disappeared soon after discontinuation of the stimulation [Bauer 2016].

6.4 Summary of known and potential risks and benefits

To date t-VNS has been well tolerated, without any serious adverse events. The most common side effects are headache and skin irritation and occur in 10-20%.

6.5 Description and justification of route of administration and dosage

According to the intended use, the stimulation is transcutaneous at the site of the external ear. The device parameters correspond to the advised settings by the producer and used in the published trials [Bauer 2016, Stefan 2012].

6.6 Dosages, dosage modifications and method of administration

The device will be used in the condition, and with the settings as supplied by the producer. The subject only has the ability to adjust the applied current. The current is set just below the threshold value for painful stimulation (paraesthesia) according to intended use which is also applied in previous trials.

6.7 Preparation and labelling of Investigational Medicinal Product

Since the investigational product is not pharmaceutical, the GMP guidelines are not relevant for this study.

6.8 Drug accountability

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

All patients will receive standard medical care for refractory focal epilepsy, in this case treatment with add-on Brivaracetam 2dd 50mg in accordance to guidelines.

7.1 Name and description of non-investigational product(s)

Brivaracetam (BRV, Briviact. UCB Pharma, Belgium) is a ligand of the synaptic vesicle protein SV2A, and approved for adjunctive treatment of focal seizures in adults. SV2A is a membrane glycoprotein and galactose transporter, present throughout the central nervous system in both GABA-ergic and glutaminergic neurons. It has been suggested that SV2A regulates several steps in the neurotransmitter release in the synaptic vesicle cycle. The anticonvulsant properties of BRV are thought to be a result of binding to SV2A and thus modulating neurotransmitter release [Klein 2018].

7.2 Summary of findings from non-clinical studies

In phase I studies BRV was well tolerated and had a favourable pharmacokinetic profile over a wide dose range [Klein 2018]. BRV is highly lipid soluble and shows a rapid brain penetration. After oral administration, BRV is rapidly absorbed with a time to maximum concentration of approximately 1 hour. The maximum tolerated dose in healthy volunteers was 1,000 mg. Pharmacokinetics were not affected by age in healthy volunteers. Most patients with refractory epilepsy will use one or more AEDs. Brivaracetam does not influence the CYP system, thus little interaction is expected with other AEDs the patient is already using. Furthermore, BRV did not significantly affect steady-state plasma concentration levels of concomitant AED's in a large study of adult epilepsy patients [Benbadis 2018]. Treatment initiation can take place at target dose, without a titration period.

7.3 Summary of findings from clinical studies

Safety, tolerability and efficacy has been proven in 3 phase III prospective, multicentre, randomized, double-blind, placebo-controlled trials using a dose range of 50-200 mg/day in the adjunctive treatment of refractory focal seizures [Klein 2018]. A pooled analysis of these trials showed a significant reduction over placebo in focal seizure frequency/28 days and $\geq 50\%$ responder rates respectively of 19.5% and 34.2% for BRV 50mg/day, 24.4% and 39,8% for 100mg/day, and 24% and 37,8% for 200mg/day. In a significant percentage

of patients efficacy is seen as early as the first week of treatment and the effect continues to exist in the long-term.

7.4 Summary of known and potential risks and benefits

Treatment adverse effects (TEA) of BRV were studied using a pooled long term follow up of the 3 phase III clinical studies, investigating a total BRV exposure of 5,339 patient years. Most frequent TEA's were headache (20.9%), dizziness (17.5%), somnolence (15.2%), nasopharyngitis (13.2%), fatigue (11.3%) and convulsions (10.6%) [Klein 2018]. Suicidal ideation was present in 0.5%. Discontinuation because of TEA's was seen in 5.0%, 7.6% and 6.8% of patients treated with 50, 100, and 200mg BRV per day. Suicidal ideation was seen in 0.2% of patients taking BRV versus 0.7% in the placebo-group, with no reports of suicide attempts.

7.5 Description and justification of route of administration and dosage

Brivaracetam will be administered orally according to the intended use.

7.6 Dosages, dosage modifications and method of administration

The starting dosage is 50mg two times daily and the dose adjustments, up to a maximum of 200mg daily, will be done by the treating neurologist corresponding to standard medical care.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable, as the medication is prescribed and supplied outside the study.

7.8 Drug accountability

Not applicable, as the medication is prescribed and supplied outside the study.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The success of therapy in epilepsy is not only determined by the amount of seizures, but by a combination of factors, for example cognitive disturbances, quality of life, the amount of side effects of treatments, society participation [Blond 2016, Baker 2011, Chaplin 1998]. Moreover, vagus nerve stimulation not only has an effect on seizures, but also on, for instance, cognitive performance [Groves & Brown 2005, Vonck et al 2014]. Therefore, we chose to use a compensatory index to determine the degree of success of therapy (Table 1).

Table 1

Compensatory index	
Seizure reduction $\geq 50\%$	3p
Processing speed improvement $\geq \frac{3}{4}$ SD	2p
QL-VAS improvement (appendix 1) ≥ 2 points	1p

8.1.2 Secondary study parameters/endpoints

- Seizure reduction in % at 3 and 6 months in respect to baseline compared between treatment groups
- Seizure freedom rates
- Seizure severity assessed by the National Hospital Seizure Severity Scale – NHS3 [O’Dhonogue 1996], appendix 2
- Profile Of Mood State short form (POMS-SF) questionnaire to assess mood state, appendix 3
- Respons in the primed group correlated with resilience assessed by the Connor-Davidson resilience scale, appendix 4
- (Improvement in) cognitive functioning assessed by computerised cognitive tasks
- Improvement of quality of life in multiple domains (QOLIE-10-P), appendix 5

- Number of adverse events ascribed to tVNS and brivaracetam measured with the SIDAED questionnaire, **appendix 6.**
- Change in network properties at 3 and 6 months

8.1.3 Other study parameters (if applicable)

By using randomisation we hope to reduce the effect of **confounding**, for example the effect of age (**bijv lagere leeftijd meer plasticiteit mogelijk waarbij meer effect tVNS?**)

Dosis medicatie hierin nog een factor?

More than 2 prior AED's? of exclusive criteria?

Uitlokkers epilepsie zoals stress, ziekte, slaaptekort

Type epilepsie: met of zonder secundaire generalisatie?

<Please describe the other study parameters. For example, baseline values or parameters which might intervene with the main study parameter (confounders), like body weight, smoking, etcetera. >

8.2 Randomisation, blinding and treatment allocation

Subjects are randomised by the investigators using randomisation software. Both patient, investigator and treating neurologist are not blinded, because of lacking a true sham stimulation protocol.

8.3 Study procedures

Screening Visit

Prior to formal enrolment, the treating neurologist will screen interested subjects and determine if they meet inclusion, and no exclusion criteria. Eligible subjects will be provided with study information and informed consent documents in compliance with the local regulatory and legal requirements. Conform regular treatment subjects are educated by their neurologist about brivaracetam, and the medication is started.

Baseline Visit (V1)

The investigator will read the informed consent and discusses the study information with the subject. If the subject meets inclusion and exclusion criteria, and agrees to participate, their signature will be obtained in duplicate on the informed consent. The subject will be educated on how to classify seizures and maintain a seizure calendar. Questionnaires (Qolie-10-p, NHS3, Raven, POMS-SF and resilience) will be completed. MRI scan and neuro cognitive tests will be performed. Randomisation will be performed. The tVNS group will be educated about the device which will also be demonstrated.

Telephone call 1 (T1) for tVNS group

The week following the start of the tVNS, usability issues are evaluated.

Seizure frequency and severity

Patients will track and record their seizures by means of the epilepsy module in the mobile device application MedApp co-developed by Nationaal epilepsiefonds. In absence of a mobile device patients will use a paper seizure diary. This data will be evaluated every four weeks through either telephone calls (T2-5) or the visits (V1-3). Assessment of adequate treatment with brivaracetam and possible dose adjustments of brivaracetam as a consequence will be carried out by the treating neurologist in accordance to normal health care at visit 2 and 3 (V2-3). The seizure severity questionnaire will be completed during the visits (V1-3).

Questionnaires

Besides seizure severity, the quality of life and mood questionnaires will be completed during the visits (V1-3), the resilience questionnaire only during the first visit.

Adverse events and side effects

This data will also be evaluated all contact moments (by means of the SIDAED questionnaire), and patients are also able to mark them in MedApp. Any change in the treatment policy because of these effects is up to the treating neurologist.

MRI protocol

At baseline, 3 months and 6 months patients will undergo a MRI scan with sequences for structural imaging (T1, T2, FLAIR), diffuse tensor imaging (DTI) and resting state fMRI

to display structural and functional connectivity. Contra-indications for MRI imaging are included in the exclusion criteria for the study. **Evt nog spectro toevoegen.**

Neuro cognitive tests

The cognitive test battery comprises three cognitive tasks displayed on a Tobii computer with integrated eye tracker that records the performance. Three cognitive tasks will be displayed:

1. Computerized visual searching task (CVST) (Aldenkamp 2004): Subjects have to compare a centered grid pattern with 24 surrounding patterns, one of which is identical to the target pattern. The test consists of 24 trials. Conventional output score is the total average searching time in seconds.
2. Binary choice reaction test (BKT): Subjects have to react differentially to a red square, presented on the left side of the screen than to a green square, presented on the right side. The score is the reaction time in milliseconds.
3. Visual reaction time (VRT): Subjects have to react as quickly as possible to a simple visual stimulus (white square on the screen) that is presented at random intervals, by pressing on the spacebar.

The total duration of the test is ... minutes.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. For instance, in case of prolonged hospitalization or seizure exacerbation with needs of addition of antiepileptic medication (except rescue medication) the subject will receive the necessary medical treatment but will be withdrawn from the study. For ethical reasons, if the subject wishes to continue t-VNS after withdrawal from the study this is allowed for the specified period.

8.5 Replacement of individual subjects after withdrawal

When a participant is withdrawn from the study, the subject will not be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Special follow-up for participants who are withdrawn from treatment is not considered necessary.

8.7 Premature termination of the study

If the **interim analyses** demonstrates statistically significant results that answer the primary research questions, inclusion will be halted. We expect no serious adverse effects other than the known mild side effects of treatment with BRV or t-VNS which could cause a premature termination of the study.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigators will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigators will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the tVNS. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

We expect no SAEs in this study. In the unlikely case a SAE will occur, the study will be aborted until a possible connection between the SAE and our study is ruled out.

The sponsor will report the SAEs through the webportal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

SUSARs will be handled conform SAEs.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the investigators will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable

10. STATISTICAL ANALYSIS

The analysis will be performed using SPSS, using Ancova, with the baseline assessment as covariate, comparing the two delta's of the two treatment arms. For further explanatory analysis we will use linear regression and discriminant analysis.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (as adopted by the 59th WMA General Assembly, Seoul, October 2008), and in accordance with the medical Research Involving Human Subjects Act (WMO) and in compliance with all laws and regulation of Epilepsy Centre Kempenhaeghe, Heeze, the Netherlands, when applicable for this study.

11.2 Recruitment and consent

Oral and written information about the aims of the study and the procedures will be provided by the patients' neurologist or the investigators during the baseline visit when BRV is started. They will have the possibility to contact an investigator during working hours, and there will be an opportunity for questions during the first visit. An example of the patient information letter and informed consent can be find in the attachments (Appendix 7).

11.3 Objection by minors or incapacitated subjects

No minors or incompetent adults will be included in this study.

11.4 Benefits and risks assessment, group relatedness

If the treatment with tVNS is effective at this stage of treatment this potentially prevents burden of more additional anti-epileptic drugs, invasive methods of BS or surgery. The increase of quality of life and decrease of seizures, or even achieving seizure freedom, has an immense value because of medical, emotional, social and economic consequences. And above all, this is then applicable to tens of thousands patients in the Netherlands alone. Moreover, because tVNS is not only used for epilepsy, the increase of information about its working mechanism might be beneficial for other brain disorders as well.

Equally important, to this point no severe harm is demonstrated because of tVNS use. If the known mild side effects occur, these are temporary in nature and will disappear after discontinuation of tVNS.

11.5 Compensation for injury

The sponsor/investigator has a liability **insurance** which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Patients may declare the costs made for travelling to and from Kempenhaeghe and will receive a gift of €25 to thank them for their voluntary participation.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data are handled confidentially and anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list can be used to link the data to the subject. The principle investigator will safeguard the key to the code. The data will be stored for a period of 15 years. The handling of personal data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). Unsuspected relevant findings on MRI will always be communicated with the general practitioner.

12.2 Monitoring and Quality Assurance

Not applicable.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year of the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

We intend to publish the findings from the current study in international, peer-reviewed journals. Publication will not be limited to positive findings.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

*For registered products to be used within the indication and **not** in combination with other products chapter 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >*

a. Level of knowledge about mechanism of action

The exact working mechanism of tVNS and VNS is not known yet (see chapter 1 and 6). So far, different hypotheses have been suggested for the working mechanism of BS in general or VNS, of which none have been definitely proven by this day. Both actions at neuron and network level are described. Moreover, if the working mechanism of tVNS corresponds to invasive VNS is not known either, but the first studies at least don't prove otherwise. Except for the different side effects due to the stimulation site.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

tVNS is already tested in multiple trials with epilepsy patients (see chapter 6). Additionally, tVNS is used in multiple healthy subjects and patients with other diseases, for example tinnitus, headache disorders or psychiatric diseases (Van Leusden et al 2015, Ben Menachem et al 2015, Wu et al 2018, Yakunina 2018). Furthermore, there are many years of experience with VNS and there is no reason to believe that tVNS has a very different working mechanism based on the so far published trials (see chapter 6).

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

There are animal studies describing the effect of tVNS (see chapter 6), but those studies are not sufficient to answer the objectives because the differences in animal brain and behaviour compared to humans, among other things.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Besides the diseased part of the brain other brain areas are targeted too, of which no disadvantageous effects are known and expected. On the contrary, the reported positive effects on cognition might be partly caused by this. Target organs of the vagal nerve, for example the heart, possibly experience an effect of tVNS. However, so far no systemic

side effects are reported in tVNS (see chapter 6). To be sure, patients with known cardiac arrhythmias are excluded.

e. Analysis of potential effect

The known side effects are mild and temporary of nature, and disappear immediately after discontinuation of tVNS (see chapter 6).

f. Pharmacokinetic considerations

Not applicable.

g. Study population

Subjects are patients suffering from refractory focal epilepsy of unknown etiology which is usually not life-threatening. There is a chance of so called sudden unexpected death in epilepsy (SUDEP) which is estimated at 9 in 1000 patient years in epilepsy patients in general, but is more prevalent in patients with nocturnal and generalised seizures which occur less frequently in focal epilepsy of unknown etiology.

h. Interaction with other products

We hypothesize that the effect of BRV is strengthened by tVNS, but this expectation is mostly theoretical and partly based on studies in patients with other (in particular psychiatric) brain diseases with different medication and/or stimulation protocols, so the exact mechanism is not known.

i. Predictability of effect

Since the exact mechanism is not known we investigate multiple outcome measures in both seizure reduction, cognitive improvement and quality of life, based on previous trials (see chapter 6). Since many outcome measures are subjective to reporting by patients, we also look for quantitative measures with MRI and computerized cognitive tests.

j. Can effects be managed?

No direct antagonist of tVNS is known, besides stopping the stimulation. In case of acute seizure exacerbation, which is not expected, management is possible with different fast working medicaments such as benzodiazepines.

13.2 Synthesis

<should include uncertainties and the unknown and the overall risk:

Make clear what measures have been taken to reduce what risks

Make clear why in your opinion the remaining risks are acceptable for the subjects participating in the study>

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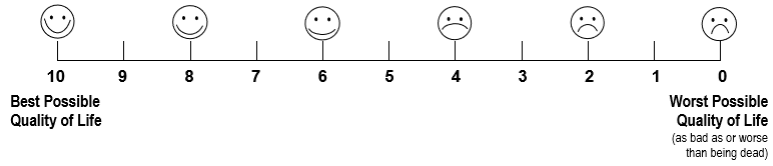
Wu 2018

Yakunina 2018

15. APPENDIX

15.1 QL-VAS

Overall, how would you rate your quality of life?
(Circle one number on the scale below)



15.2 NHS3

M. F. O'DONOGHUE ET AL.

THE NATIONAL HOSPITAL SEIZURE SEVERITY SCALE - NHS3

Patient's name:

Date:

Instructions for completion:

1. Define how many different types of seizure occur (e.g. aura, complex partial, generalized convulsion...). Call these type 1-3 arbitrarily.

2. Apply questions 2-8 to each seizure type separately. As the NHS3 indicates current seizure severity, define the time frame: e.g. 1-3 months or time since the last clinic visit. Use clinical judgment whether each factor occurs in the seizure type (i.e., the physician decides if there is a convulsion after questioning the patient). Allow the patient to judge the frequency of each event. Then tick the box opposite the response options. The number in the box is the score for that question.

Note:
Q.3. Only actual falls are recorded i.e. if the seizures could cause falls but have not because they all occurred while in bed, then the score is 0.
Q.7 refers to the time until the patient feels fully functional.
Note the specific scoring instructions for Q4. and 6.

3. The column totals give the seizure severity score.

	Type 1	Type 2	Type 3
1. Record the name of the seizure types that occur under headings "type1,2,3...."			
<i>since the last visit:</i>			
2. Does the patient have a generalized convulsion during this type of seizure ?			
Yes	4	4	4
No	0	0	0
3. How often has the patient fallen to the ground in this type of seizure ?			
Nearly always or always	4	4	4
Often	3	3	3
Occasionally	2	2	2
Never	0	0	0
4. Has this type of seizure caused any of the following ? (score only the worst)			
Burns,scalds, deep cuts, fractures	4	4	4
Bitten tongue or severe headaches	3	3	3
Milder injuries or mild headaches	2	2	2
No injuries	0	0	0
5. How often has the patient been incontinent of urine in this type of seizure ?			
Nearly always or always	4	4	4
Often	3	3	3
Occasionally	2	2	2
Never	0	0	0
6. If the seizure causes loss of consciousness, is there a warning long enough for the patient to protect him/herself ? (no loss of consciousness or seizures only while asleep scores 0)			
Never	2	2	2
Sometimes	1	1	1
Nearly always or always	0	0	0
7. How long is it until the patient is really back to normal after the seizure?			
Less than 1 minute	0	0	0
Between 1 and 10 minutes	1	1	1
Between 10 minutes and 1 hour	2	2	2
Between 1 and 3 hours	3	3	3
More than 3 hours	4	4	4
8. Do the following events occur in this type of seizure ?			
Seriously disruptive automatisms (e.g. shouting, wandering, undressing)	4	4	4
Mild automatisms or focal jerking	2	2	2
None	0	0	0
Add 1 point to each column	1	1	1
TOTAL SCORE FOR EACH SEIZURE TYPE			

15.3 Connor-Davidson Resilience Scale

CONNOR-DAVIDSON RESILIENCE SCALE (CD-RISC)^{DUTCH} (CD-RISC-25^{DUTCH}) ©

Zet bij elke vraag een kruisje in het vakje dat het beste aangeeft in hoeverre u eens bent met de stelling – het gaat om de afgelopen **maand**.
Als een bepaalde situatie zich niet recent heeft voorgedaan, geef dan antwoord hoe u denkt dat u zich gevoeld zou hebben.

	Helemaal niet waar (0)	Zelden waar (1)	Soms waar (2)	Vaak waar (3)	Bijna altijd waar (4)
1. Ik ben in staat om me aan te passen als er veranderingen optreden.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Ik heb met minstens één persoon een dusdanig goede en bestendige band dat die mij helpt als ik gestrest ben.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Als er geen duidelijke oplossingen zijn voor mijn problemen, kan soms het lot of God mij helpen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Ik kan goed omgaan met alles wat op mijn pad komt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Successen uit het verleden geven mij zelfvertrouwen bij het omgaan met nieuwe uitdagingen en moeilijkheden.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Ik probeer de humoristische kant te zien als ik met problemen word geconfronteerd.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Het hoofd bieden aan stressvolle situaties kan me sterker maken.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Ik heb de neiging om weer op te veren na ziekte, blessures of andere moeilijke situaties.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Ik geloof dat de meeste dingen gebeuren met een reden, of het nu goede of slechte dingen zijn.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Ik doe mijn uiterste best, ongeacht de uitkomst.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Ik geloof dat ik mijn doelen kan bereiken, zelfs als er obstakels zijn.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Zelfs als alles er hopeloos uitziet, geef ik niet op.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Als ik in een stress-situatie of crisissituatie verkeer, weet ik waar of bij wie ik hulp kan krijgen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Als ik onder druk sta, blijf ik mijn doel voor ogen houden en helder nadenken.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Ik geef er de voorkeur aan om zelf de touwtjes in handen te houden bij het oplossen van problemen, en niet anderen alle beslissingen te laten nemen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Ik laat me niet snel uit het veld slaan bij tegenstagen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Ik zie mezelf als een sterke persoon bij het omgaan met de uitdagingen en moeilijkheden in het leven.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Ik kan moeilijke en voor anderen mogelijk ingrijpende beslissingen nemen als het moet.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Ik kan omgaan met onplezierige gevoelens als verdriet, angst en boosheid.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Bij het omgaan met de problemen in het leven, moet je soms afgaan op je intuïtie, ook al weet je niet waarom.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Ik heb sterk het gevoel dat het leven een bedoeling heeft.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Ik voel me zelf aan het roer staan in mijn eigen leven.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Ik houd van uitdagingen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Ik werk om mijn doelen te bereiken, ongeacht het aantal belemmeringen, dat ik onderweg tegenkom.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Ik ben trots op mijn prestaties.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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15.4 QOLIE-10-P

15.5 POMS-SF

15.6 SIDAED

15.7 Patient information form and informed consent