Tampere University

TONI KULJU

VNS Therapy for Refractory Epilepsy

Tampere University Dissertations 303

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ACADEMIC DISSERTATION
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ABSTRACT

Background: More than 50 million people worldwide suffer from epilepsy, and approximately 30% of them are considered as drug-resistant (refractory), as the seizures are not in control with two adequately used antiepileptic drug schedules. Vagus nerve stimulation (VNS) is a promising treatment option for these patients. Neuromodulation therapies in the treatment of epilepsy are under substantial research, and the mechanisms of actions and details of function are still not fully understood.

Aims: The purpose of this study is to elucidate the functions of VNS therapy including the efficacy and the details concerning the automatic stimulation (responsive VNS, rVNS) properties. Other goals are to assess the power usage aspects of the treatment with different settings and after initiating automatic stimulation mode, and to gain a better understanding of the behavior of responsive stimulations in epilepsy patients.

Materials and Methods: Altogether 42 patients with refractory epilepsy were included in four studies. Follow-up time was highly variant, from 13 days to more than 11 years. The clinical and stimulation-related data were analyzed with SPSS, Excel, and Matlab softwares. We used nonparametric statistical tests and elucidated the results with illustrations.

Results: In the first study we found that in 90% of the patients the response to ANT-DBS (deep brain stimulation of the anterior nucleus of the thalamus) therapy was similar to VNS therapy (progressively better, partial response, no response) in patients with refractory epilepsy. In the second study, we found the initiation of automatic stimulation mode leading to better seizure control in 36.4 % of the patients. Therefore we were able to alter other stimulation settings, which led to significantly reduced battery usage. In the third study, we confirmed the altered stimulator settings affecting the number of stimulations and total charge delivered in the patient, especially when altering the OFF-time and the autostimulation threshold, and a possible difference between the function of rVNS in the temporal lobe and other epilepsy patients. In the fourth study, we found circadian patterns in automatic stimulations in most of the patients resembling the pattern of cortisol secretion. Our results support the finding that response to VNS therapy improves over time.

Conclusions: Vagus nerve stimulation is a promising treatment option for patients with refractory epilepsy. The automatic stimulation mode of VNS offers better seizure control with possibly lesser power usage than the older models. The responses to VNS and ANT-DBS therapies show similarities. There is circadian rhythmicity in the autostimulation activations in rVNS therapy. Shortening the OFF-time and lowering the threshold rate leads to a larger number of stimulations delivered.

Keywords: VNS, vagus nerve stimulation, automatic stimulation, refractory, epilepsy, treatment, responsive, neurostimulation

TIIVISTELMÄ

Tausta: Epilepsiaa sairastaa maailmanlaajuisesti yli 50 miljoonaa ihmistä, ja heistä 20-30%:lla kyseessä on vaikeahoitoinen epilepsia, eivätkä kohtaukset ole hallinnassa kahdella oikein käytetyllä epilepsialääkkeellä. Vagushermostimulaatio (VNS) on verrattain uusi hoitovaihtoehto näille potilaille, ja tulokset hoidon tehosta ovat lupaavia. Neuromodulaatiohoitoja tutkitaan laajasti, eivätkä toimintamekanismit tai tarkempi ymmärrys laitteiden toiminnasta ole selviä.

Tavoitteet: Väitöskirjassa selvitetään VNS-hoidon toimintaa ja tehokkuutta erityisesti automaattiseen stimulaatioon (rVNS, responsiivinen VNS) liittyen. Lisäksi tavoitteena on selvittää laitteen virrankulutusta suhteessa käytettyihin asetuksiin ja automaattisen stimulaation käyttöönottoon, sekä saada tietoa automaattisten stimulaatioiden käyttäytymisestä epilepsiapotilailla.

Materiaalit ja menetelmät: Yhteensä 42 vaikeahoitoista epilepsiaa sairastavaa potilasta sisällytettiin neljään tutkimukseen. Seuranta-aika vaihteli laajasti, kolmestatoista päivästä yli yhteentoista vuoteen. Kliiniset ja stimulaatioihin liittyvät tiedot analysoitiin SPSS-, Excel- ja Matlab -ohjelmistoilla. Käytimme ei-parametrisia tilastollisia testejä ja havainnollistimme tuloksia kuvaajilla.

Tulokset: Ensimmäisessä tutkimuksessa havaitsimme samankaltaisuuksia vasteissa VNS- ja ANT-DBS (talamuksen anteriorisen tumakkeen syväaivostimulaatio) -hoitoihin 90%:lla vaikeahoitoista epilepsiaa sairastavilla potilaista (progressiivinen paranema, osittainen vaste, ei vastetta). Toisessa tutkimuksessamme havaitsimme automaattisen stimulaation tuovan lisävastetta VNS-hoitoon 36.4 %:lla potilaista, jolloin normaalistimulaation asetuksia pystyttiin muuttamaan, mikä johti virrankulutuksen merkittävään vähenemiseen. Kolmannessa tutkimuksessa varmensimme, että asetuksia, erityisesti OFF-aikaa ja autostimulaation kynnystä, muuttamalla voidaan vaikuttaa stimulaatioiden määrään ja laitteen virrankulutukseen, sekä havaitsimme eroavaisuuksia automaattisen stimulaation toiminnassa ohimolohkoepilepsiaa ja muita epilepsioita sairastavien potilaiden välillä. Neljännessä tutkimuksessa havaitsimme, että suurimmalla osalla potilaista automaattisten stimulaatioiden vuorokausittainen vaihtelu muistuttaa kortisolintuotannon vuorokausittaista rytmiä. Lisäksi tuloksemme tukevat hypoteesia VNS-vasteen kehittyvästä luonteesta ajan kuluessa.

Johtopäätökset: Vagushermostimulaatio on lupaava hoitovaihtoehto vaikeahoitoista epilepsiaa sairastaville potilaille. Automaattisen stimulaation käyttöönotto johtaa parempaan kohtausten hallintaan mahdollisesti vähäisemmällä virrankulutuksella. VNS- ja ANT-DBS -hoitojen vasteissa on samankaltaisuuksia. Automaattisen stimulaation toiminnassa on vuorokautinen vaihtelu. OFF-ajan lyhentäminen ja autostimulaation kynnyksen laskeminen johtaa suurempaan stimulaatioiden määrään.

Avainsanat: VNS, vagushermostimulaatio, automaattinen stimulaatio, vaikeahoitoinen, epilepsia, hoito, responsiivinen, neurostimulaatio

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ABBREVIATIONS

18F-FDG PET	18F-fluorodeoxyglucose positron emission tomography
5-HIAA	5-hydroxyindoleacetic acid
6-OHDA	6-hydroxydopamine
ABR	arterial baroreflex
ACC	anterior cingulate cortex
ACTH	adrenocorticotropic hormone
AED	antiepileptic drug
AEG	antiepileptogenesis
ANS	autonomic nervous system
ANT	anterior nucleus of the thalamus
AutoStim	automatic stimulation mode of VNS
AV	atrioventricular
BDI	Beck's depression inventory
Ca	calcium
CAR	cortisol awakening response
CC	corpus callosotomy
CI	confidence interval
CNS	central nervous system
CPAP	continuous positive airway pressure
CRS-R	coma recovery scale-revised
CRH	corticotropin-releasing hormone
CT	computed tomography
DBS	deep brain stimulation
DRE	drug-resistant epilepsy
DRN	dorsal Raphe nucleus
ECG	electrocardiography
EEG	electroencephalography
EMA	European Medicine Agency
EMU	epilepsy monitoring unit
ETLE	extratemporal lobe epilepsy

f	frequency
FAS	focal aware seizure
FBTCS	focal to bilateral tonic-clonic seizure
Fc	functional connectivity
FDA	US Food and Drug Administration
FES	focal epileptic spasm
FIAS	focal impaired awareness seizure
FLE	frontal lobe epilepsy
fMRI	functional MRI
FMS	focal motor seizure
FNMS	focal nonmotor seizure
GABA	gamma-aminobutyric acid
GAS	generalized absence seizure
GES	generalized epileptic spasm
GMS	generalized motor seizure
GTCS	generalized tonic-clonic seizure
HR	heart rate
HRV	heart rate variability
HPA	hypothalamic-pituitary-adrenal
Hz	Hertz
I	output current
IBE	International Bureau of Epilepsy
IED	interictal epileptiform discharge
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
KD	ketogenic diet
K-Wt	Kruskal-Wallis test
L-VNS	left-sided VNS
LC	locus coeruleus
MFE	multifocal epilepsy
MER	microelectrode recording
MES	maximal electroshock
MRI	magnetic resonance imaging
M-Wt	Mann-Whitney test
Na	sodium
NE	norepinephrine

NHS3	National Hospital Seizure Severity Scale
NTS	nucleus tractus solitarius, the nucleus of the solitary tract
OLE	occipital lobe epilepsy
ON%	therapy time
pdBSI	pairwise derived brain symmetry index
PBN	parabrachial nucleus
PLE	parietal lobe epilepsy
PNES	psychogenic nonepileptic seizure
Pw	pulse width
Q	charge
QOLIE-31-P	Quality of Life in Epilepsy-Patient-Weighted
RCT	randomized controlled trial
R-VNS	right-sided VNS
rVNS	responsive VNS
SA	sinoatrial
SCD	sudden cardiac death
SCP	slow cortical potential
SD	standard deviation
SMR	standardized mortality rate
SP	stimulation period
SSQ	Seizure Severity Questionnaire
SUDEP	sudden unexpected death in epilepsy
SV2A	synaptic vesicle binding protein 2A
TRD	treatment-resistant depression
T	time
TLE	temporal lobe epilepsy
TWA	T-wave alternans
UTCS	unknown onset tonic-clonic seizure
V	volt
VNS	vagus nerve stimulation

ORIGINAL PUBLICATIONS

Publication I Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Kulju T, Haapasalo J, Lehtimäki K, Rainesalo S, Peltola J. Brain Behav. 2018;8(6):e00983.

Publication II Autostimulation in Vagus Nerve Stimulator Treatment: Modulating Neuromodulation. Kulju T, Haapasalo J, Rainesalo S, Lehtimäki K, Peltola J. Neuromodulation Technol Neural Interface. 2019;22(5):630-637.

Publication III Frequency of automatic stimulations in responsive vagal nerve stimulation in patients with refractory epilepsy. Kulju T, Haapasalo J, Verner R, Dibué-Adjei M, Lehtimäki K, Rainesalo S, Peltola J. Neuromodulation Technol Neural Interface. 2020;23:852-858.

Publication IV Circadian distribution of autostimulations in rVNS therapy in refractory focal epilepsy patients. Kulju T, Verner R, Dibué-Adjei M, Eronen A, Rainesalo S, Lehtimäki K, Haapasalo J, Peltola J. Epilepsy Behav. 2020 May 27;110:107144. Online ahead of print.

1 INTRODUCTION

Epilepsy is the most common neurological disease affecting individuals all around the world of all ages. Worldwide, as many as 50 million people, or 1% of the population, suffer from epilepsy (Banerjee et al., 2009, Singh et al., 2016). Up to 30% of patients are considered to have drug-resistant (also known as refractory or intractable) epilepsy (Kwan and Brodie, 2000, Kwan et al., 2009).

To this day there have been more than 40 different antiepileptic drugs introduced, over a time span of more than 150 years, with several different mechanisms of action. (Schmidt et al., 2014). In some patients with refractory epilepsy, the treatment of choice would be epilepsy surgery often leading to complete seizure freedom. The surgery options are resective or nonresective/disconnection procedures. (Englot et al., 2014, Englot et al., 2017). The most of the focal refractory epilepsy patients are not amenable for the epilepsy surgery (Cloppenborg et al., 2016). Therefore, neurostimulation therapies have been arising palliative treatment options for these patients, with promising results and tolerable side effects and complications.

The principle of Vagus Nerve Stimulation (VNS) is to deliver electrical current to the brain via the tenth cranial nerve, *nervus vagus*. The specific mechanisms of actions are still not fully understood. The programmable pulse generator is implanted into the upper chest under the skin and the electrodes are wrapped around the left vagus nerve. VNS has been reported to reduce seizure frequencies for more than 50% in 30% (Ryvlin et al., 2014), to 50-60% (Cukiert, 2015, Elliott et al., 2011) of the patients with refractory epilepsy. The long-term efficacy for VNS-therapy improves progressively (Englot et al., 2016, Révész et al., 2018, Wang et al., 2019). The patients are also equipped with a wrist-worn magnet to provide additional stimulations when noticing an emerging seizure, or to pause the action of the VNS device. The model 106 (AspireSR®, LivaNova, Houston, TX, USA) of VNS also provides an automatic stimulation option based on the algorithm detecting ictal tachycardia and thus automatically triggering additional stimulations when emerging or ongoing seizures are detected (Hampel et al., 2015).

In Deep Brain Stimulation (DBS), the electrodes are stereotactically implanted into the brain, directly to the stimulation site; in epilepsy patients usually into the

anterior nucleus of the thalamus (ANT-DBS) (Sprengers et al., 2014, Zangiabadi et al., 2019). The pulse generator is implanted into the upper chest. (Lehtimäki et al., 2016). According to the pivotal studies, in 2 years, 54% of the patients were responders with at least a 50% reduction in seizure frequency, and the response improves over time (Fisher et al., 2010, Salanova et al., 2015).

Existing evidence suggests of rhythmicity in seizure occurrence, forming circadian and ultradian patterns; e.g. correlation with cortisol secretion or seizure-onset-dependent patterns, especially in temporal lobe and frontal lobe onset seizures (Spencer et al., 2016, van Campen et al., 2015, Pavlova et al., 2004). As sudden unexpected death in epilepsy is considered to be a nocturnal phenomenon, sudden cardiac deaths occur usually in the morning (Ali et al., 2017, Muller et al., 1987).

Despite the known efficacy of VNS, the mechanisms of action and detailed knowledge of the performance are not elucidated. It is still not clear how to program the stimulator to achieve the best possible outcome, and it has not been elucidated yet, how altering the stimulator settings would result in autostimulation performance and power usage. Although there are several studies about circadian and ultradian patterns in epileptic seizure occurrence, these things are not been assessed in autostimulation behavior. Also, the similarities between these two neuromodulation therapy options are not clear.

Purpose of this study is to investigate a part of these unanswered questions regarding to VNS therapy.

2 REVIEW OF THE LITERATURE

2.1 Epilepsy

2.1.1 Epidemiology

Epilepsy is the most common neurological disease affecting individuals all around the world of all ages. 50 million people worldwide suffer from epilepsy. In the meta-analysis of Fiest et al. (2017), comprising a total of 222 studies, the following rates were presented; the prevalence of active epilepsy is 6.38 per 1,000 persons (95% confidence interval (CI) 5.57–7.30), while the lifetime prevalence is 7.60 per 1,000 persons (95% CI 6.17–9.38). The annual cumulative incidence of epilepsy is 67.77 per 100,000 persons (95% CI 56.69–81.03) while the incidence rate is 61.44 per 100,000 person-years (95% CI 50.75–74.38). In Finland, according to the study by Keränen et al. (1989), the prevalence is 6.29 per 1000.

The incidence is higher in children: 46.90 vs 36.63 per 100,000 person years (Fiest et al., 2017). There is a tendency of incidence ratio rising along with the age in adults; the incidence in people aged from 20 to 39 years is 18 per 100 000 and in people aged from 40 to 59 years, it is 28 per 100 000, while mean annual incidence is 24 per 100 000 individuals (Banerjee et al., 2009). The prevalence do not differ by age group (Fiest et al., 2017) and the epilepsies of unknown etiology and those with generalized seizures have the highest prevalence.

In the review of Banerjee et al. (2009) the following characteristics are reported to affect the prevalence as described:

- **Age**: most reports show an increase in prevalence during adolescence or early adulthood. During adulthood, the prevalence seems to be stable and starts to increase after the age of 50. Conversely, in developing countries, the prevalence drops after the age of 50 and according to some studies, it starts increasing again after the age of 60.
- **Gender**: In the door-to-door studies the prevalence among men seems to be slightly higher. However, the difference is minimal. In addition, in some

cultures, especially women might hide the symptoms and the diagnosis due to social problems.

- **Race and ethnicity**: One study performed in Mississippi included 23 957 participants (Haerer et al., 1986). They suggest that the prevalence in the African-Americans is higher (8.2 per 1000) than in the Caucasians (5.4 per 1000). Another study suggests that the prevalence is lower in South Asians in comparison to Non-South-Asians (Wright et al., 2009).
- **Socioeconomic status**: There is no clear evidence concerning the correlation between the prevalence of epilepsy and socioeconomic status. Two studies, performed in Brazil and Zambia, suggest that the prevalence is higher among the poorer, whereas in one phone survey conducted in New York suggests that the prevalence is the highest in people with the highest income (Noronha et al., 2007, Birbeck et al., 2007, Kelvin et al., 2007). Fiest et al. (2017) concluded that the prevalence and incidence of epilepsy are higher in low to middle income countries.

2.1.2 Definitions

There have been several definitions for epilepsy and epileptic seizures over time. The conceptual and widely used definitions were published by Fisher et al. (2005), as they presented the consensus definitions for the concept of "epileptic seizure" and "epilepsy" defined by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).

Due to some drawbacks in those definitions, ILAE published a new, practical definition for epilepsy in 2014 (Fisher et al., 2014).

2.1.2.1 Definition of an epileptic seizure

> "An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain." (Fisher et al., 2005).

The word "seizure" comes from the Greek and can be translated as "to take hold". In addition to epileptic seizures, the word "seizure" can be used for any sudden and severe event. To be clear about the nature of the seizure, it can be emphasized by referring to an "epileptic seizure".

The definition criteria of epileptic seizures include the seizure being transient, causing clinical manifestations, and alterations in electroencephalography (EEG). An epileptic seizure has a clear start and end, with an exception of status epilepticus, when seizures are prolonged or recurrent.

The clinical manifestations of an epileptic seizure can be very extensive, depending on the location of the onset in the brain, patterns of propagation, the maturity of the brain, confounding disease processes, sleep-wake cycle, medications, and a variety of other factors. Seizures can affect any functional part of the brain: sensory, motor, and autonomic function; the clinical manifestations might cause symptoms to a patient's consciousness, emotional state, memory, cognition, or behavior. All the seizures have an influence on at least one of these factors. (Fisher et al., 2005).

2.1.2.2 Definition of epilepsy

In 2014 the definition of epilepsy was revised by ILAE (Fisher et al., 2014) in order to formulate an operational definition of epilepsy for purposes of clinical diagnosis.

According to the new practical definition, a person is considered to have epilepsy if they meet any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

- Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age, or those who have remained seizure-free for the last 10 years, with no anti-epileptic drugs (AEDs) for the last 5 years.

Epilepsy is often associated with several other conditions such as behavioral disturbances (e.g. inter- and postictal cognitive problems), along with the stigma, exclusion, restrictions, overprotection, and isolation caused by the disease. (Fisher et al., 2005). Also, sensory and motor defects and learning difficulties are not uncommon among patients with epilepsy.

2.1.3 Classification of seizures

ILAE published the new classification system for epilepsy in 2017 due to some imperfections in the old classification (Fisher et al., 2017). The old classification (ILAE 1981) introduced the seizure types of simple partial seizure, complex partial seizure, generalized tonic-clonic seizure, absence seizure, secondarily generalized tonic-clonic seizure, and others. There was not a proper classification for some types of seizures, and the old terms do not unambiguously describe the nature of the seizure and are only understood by the people familiarized with epilepsy. The new classification is easier to understand and to use in practice, and also the seizures fit into the categories better.

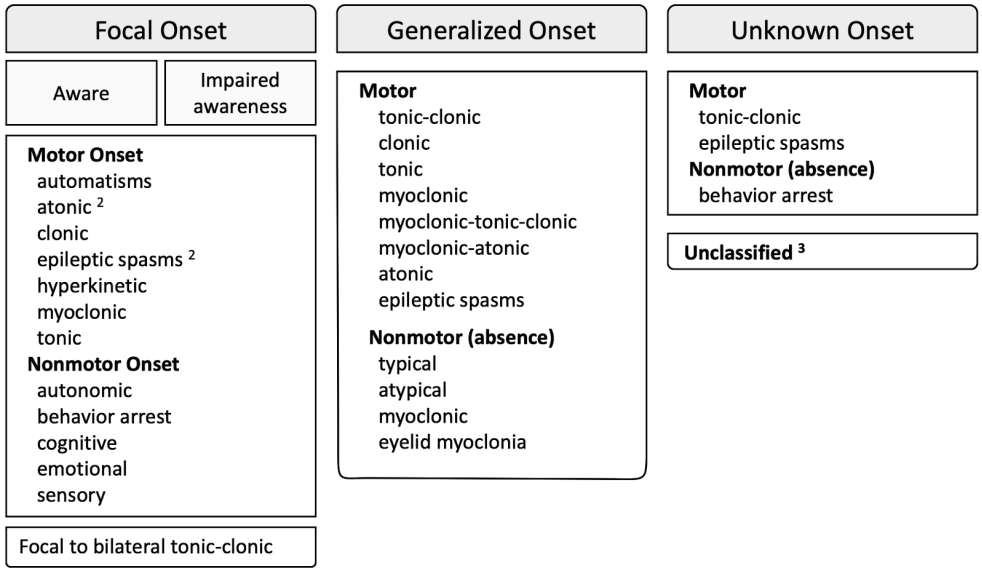
As shown in Figure 1, the seizures are first divided into three groups based on the onset; focal, generalized, and unknown onset. In the focal seizures, the definition of awareness is optional, since in some of the seizures, the awareness may be unknown, or for example, some seizures may produce emotional symptoms. The seizure is considered as aware, if a person is aware of self and environment during the seizure, even if being immobile.

Based on the first prominent sign or symptom of the seizure, the seizures may further be classified as motor-onset or nonmotor-onset seizures (Figure 1).

The generalized seizures are not divided into subgroups by awareness since the awareness is usually impaired in generalized seizures. Similar to focal seizures, also generalized seizures are divided into motor and nonmotor seizures, which also are considered as absence seizures.

If a seizure does not fit any other category or there is inadequate information, the seizure is considered as an unclassified seizure. Sometimes the onset stays unknown but the seizures may have features of motor and nonmotor seizures.

Figure 1. ILAE 2017 Classification of Seizure Types Expanded Version[1] (modified from Fisher et al., 2017). [1] Definitions, other seizure types, and descriptors are listed in the accompanying paper and glossary of terms of the original paper. [2] The degree of awareness usually is not specified. [3] Due to inadequate information or inability to place in other categories.



The abbreviations in Table 1 are suggested by ILAE (Fisher et al., 2017) for the most common seizure types. As some seizures can be characterized more accurately, there are no established abbreviations for every seizure types.

Table 1. Abbreviations of seizures (Fisher et al., 2017).

Seizure type	Abbreviation
Focal aware seizure	FAS
Focal impaired awareness seizure	FIAS
Focal motor seizure	FMS
Focal nonmotor seizure	FNMS
Focal epileptic spasm	FES
Focal to bilateral tonic-clonic seizure	FBTCS
Generalized tonic-clonic seizure	GTCS
Generalized absence seizure	GAS
Generalized motor seizure	GMS
Generalized epileptic spasm	GES
Unknown onset tonic-clonic seizure	UTCS

2.1.4 Etiology

2.1.4.1 Overview

The etiologies of epilepsy were classically divided into three main groups: idiopathic, symptomatic, and cryptogenic epilepsy along with provoked epilepsy and epileptic syndromes (ILAE 1989). However, this formerly widely used division is obsoleted. Currently, the etiologic groups of epilepsy are structural, genetic, infectious, metabolic, immune, and unknown.

2.1.4.2 Epileptogenesis

In acquired epilepsies, the process leading for the epilepsy after the insult is called epileptogenesis. Although epileptogenesis was traditionally considered as the time period between the insult and the first seizure, later research reveals that the epileptogenic processes continue even after the first seizure and the seizure frequency and severity tend to increase. Therefore, the epileptogenesis may be divided in two stages; first, the development of epilepsy and second, progression of the epilepsy. (Pitkänen et al., 2015).

Antiepileptogenesis (AEG) refers to a treatment with a goal to stop or delay the development of epilepsy, or reduce the severity of the epilepsy. Since epileptogenesis continues after the first seizure, AEG therapy may be initiated even after the diagnosis of epilepsy. (Pitkänen et al., 2015).

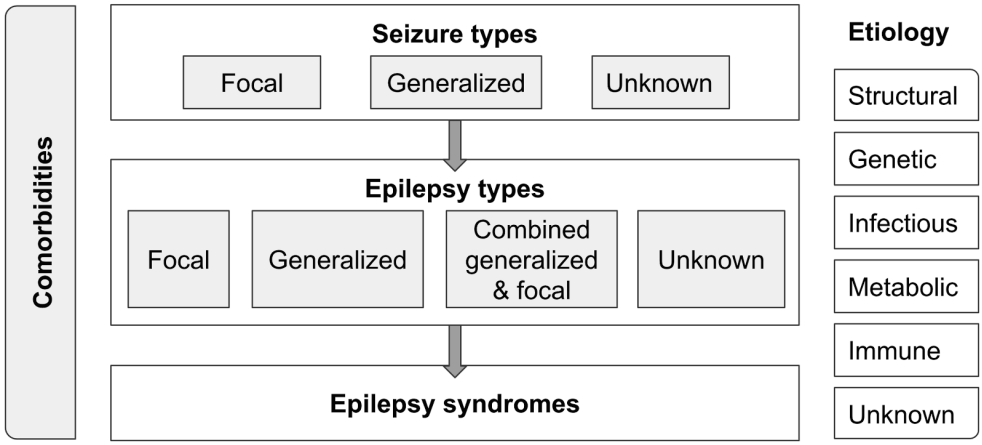
2.1.4.3 Classification of epilepsies

ILAE published a new classification for epilepsies in 2017 for standardizing the terminology and classification of epilepsies (Scheffer et al., 2017). The primary purpose of the new classification is for the diagnosis of patients, but it is also important in research and communication.

The first level of classification is the seizure type according to the new ILAE classification of seizures (Fisher et al., 2017). The second level is to diagnose the epilepsy type. The third level is an optional diagnosis for a specific epilepsy syndrome. This classification emphasizes the need to consider comorbidities and etiology at each step of diagnosis. Etiology is divided into six subgroups that are

selected due to their potential therapeutic consequences. (Scheffer et al., 2017). (Figure 2).

Figure 2. Framework for classification of the epilepsies. Modified from Scheffer et al. (2017).



2.1.5 Epileptic network

The concept of epileptic network advances the simplistic division of seizures being either focal or generalized; seizures are a consequence of a paroxysmal, pathological activation of specific neuronal connections. Epileptic seizures occur within cortical and subcortical neural networks that have different dynamical states; the interictal steady state, and ictal state with widespread synchronization. (Spencer, 2002, Holmes and Tucker, 2013).

The epileptic networks are different in different types of seizures along with individual variations. An emerging seizure may trigger the epileptiform activity in any part of the nervous system that is anatomically or functionally connected to the network; the seizure onset from several different foci may activate the same network leading to similar expression of a seizure. Therefore, assessing of the precise seizure onset zone may be irrelevant and may vary within the same patient even though the seizures would be identical. Several specific epileptic networks have been discovered. (Spencer, 2002).

The best-known epileptic network is the medial temporal/limbic network associated with the most common human refractory epilepsy. It is bilateral and cortical, involving the hippocampi, the amygdalae, the entorhinal cortices, lateral

temporal neocortices, and extratemporal components of the medial thalamus and the inferior frontal lobes. (Spencer, 2002).

The second-best known epileptic networks are the medial occipital/lateral temporal network and the superior parietal/medial frontal network. Additionally, there is evidence of existence of bifrontal/pontine/subthalamic network and the parietal/medial temporal network. (Spencer, 2002).

2.1.6 Prognosis

2.1.6.1 Response to drug therapy

The response to the first antiepileptic drug (AED) predicts the prognosis for the drug treatment distinctly. According to a study with 780 newly diagnosed patients, 504 (64.6%) of the patients became seizure-free with AED therapy for at least 12 months (Mohanraj et al., 2006). Of those patients, 462 (59.2%) remained in remission while 42 (5.4%) relapsed and later developed refractory epilepsy. The response to the first antiepileptic drug was 50.4%, to the second 10.7%, and to the third only 2.7%. Only 0.8% of the patients responded optimally to subsequent drug trials.

The study by Luciano et al. (2007) included 155 patients with chronic epilepsy that had a total of 265 drug additions. Approximately 16% of all drug additions resulted in seizure freedom at least for 12 months. In addition to that, 21% of drug additions led to a 50-99% reduction in seizure frequencies. 28% of the patients gained seizure-freedom. Fewer previously used antiepileptic drugs, shorter duration of epilepsy and idiopathic epilepsy were associated to a better response to an addition of an new AED.

2.1.6.2 Mortality

Mortality within epilepsy patients is increased when compared to the general population. The SMR (standardized mortality ratio) ranges from 1.6 to 3.0; mortality rate among epilepsy patients is increased up to threefold when compared to the general population, in every age group (Forsgren et al., 2005). According to that review, the etiology of epilepsy and the type of seizures affect the standardized mortality ratio. The lowest SMR, being quite close to the general population, is within

patients with idiopathic epilepsy (SMR 1.1 - 1.8) and highest with patients with epilepsy and neurological deficits present since birth, including intellectual disability and cerebral palsy (SMR 7 - 50), in between being symptomatic epilepsy with SMR from 2.2 to 6.5. The most important causes of death are the etiological causes for epilepsy, suicides (SMR 3.5), accidents, and status epilepticus. The most important directly epilepsy-related cause of death is SUDEP (sudden unexpected death in epilepsy) with a SMR of 23.7, which considerably reduced after epilepsy surgery. The seizure-free patients after surgery and those patients with significant palliation of tonic-clonic seizures had the lowest mortality rates. (Sperling et al., 2016).

2.1.7 Refractory epilepsy

2.1.7.1 Definition

Drug-resistant epilepsy (DRE), also known as refractory or intractable epilepsy, is commonly defined as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules, to achieve sustained seizure freedom. The AEDs can be used as monotherapy or in combination. (Kwan et al., 2009). The share of drug-resistant epilepsy patients varies between 20 and 30 percent in most of the studies (Picot et al., 2008, Kwan and Brodie, 2000, Schmidt et al., 2014).

Along with the intractable seizures, refractory epilepsy is a distinct condition with complex dimensions, like neurobiochemical plastic alterations, cognitive decline, and psychosocial dysfunctions. It often leads to dependent behavior and a restricted lifestyle, forming disabling, severe conditions. (Kwan and Brodie, 2002). The mortality among the refractory epilepsy patients is increased (Mohanraj et al., 2006).

In Finland, a definition for refractory epilepsy was refined in 2018. According to that definition, refractory epilepsy is a condition where prominent epilepsy-related symptoms are present and causing harm on the daily living despite the adequate AED therapy, such as epileptic seizures, cognitive or behavioral difficulties or adverse effects of the treatment. (Vaikean epilepsian hoidon kansallinen koordinaatioryhmä).

2.1.7.2 Mechanisms

The biological basis of refractory epilepsy is not fully understood, but it is likely to be multifactorial including an abnormal reorganization of neuronal circuitry, alteration in neurotransmitter receptors, ion channelopathies, reactive autoimmunity, and impaired antiepileptic drug penetration to the seizure focus. Some of these changes may be a consequence of seizures. (Kwan and Brodie, 2002, Kwan et al., 2011).

The main hypotheses of the mechanisms leading to refractory epilepsy are summarized below, starting from the most-cited theories. None of the theories can explain the mechanisms of pharmacoresistance alone. (Kwan et al., 2011, Tang et al., 2017).

2.1.7.2.1 Transporter hypothesis

This hypothesis suggests that overexpression of multidrug efflux transporters at the blood-brain barrier and at the epileptic focus leads to decreased AED concentrations in the targeted structure in the brain, as the drugs are transported back to the capillaries. (Tishler et al., 1995). The most studied efflux transporter is P-glycoprotein, an important component of the blood-brain barrier. In surgically removed brain specimens from refractory epilepsy patients, there is an aberrant expression of P-glycoprotein and other efflux transporters in capillaries, glial and neuronal cells. (Kwan et al., 2011, Tang et al., 2017)

A large amount of studies support the transporter hypothesis , but there are some aspects of the hypothesis that remain controversial. There is conflicting evidence regarding the P-glycoprotein expression, e.g. polymorphisms of the gene encoding P-glycoprotein might be associated with a poor response to AED therapy. (Kwan et al., 2011, Tang et al., 2017).

2.1.7.2.2 Target hypothesis

This hypothesis suggests that there would be alterations in the targets of antiepileptic drugs, such as voltage-gated ion channels and neurotransmitter receptors (Remy and Beck, 2006). In one study including patients with carbamazepine-resistant temporal-lobe epilepsy, specimens of the hippocampi were analyzed (Bien et al., 2009). The blockade effect of carbamazepine of the fast sodium channels was lost, although the

finding did not apply to lamotrigine, which has similar pharmacologic action. Altered expressions in genes encoding sodium channels and $GABA_A$ (Gamma-aminobutyric acid) receptors seem to have an association with refractory epilepsy. (Kwan et al., 2011, Tang et al., 2017).

A major weakness of this hypothesis is the lacking knowledge of the mechanism of action of antiepileptic drugs, and the evidence supports mechanisms only against a minority of AEDs (Kwan et al., 2011, Tang et al., 2017).

2.1.7.2.3 Gene variant hypothesis

In this hypothesis, an inherent pharmacoresistance is caused by variations in genes associated with AED pharmacokinetics and pharmacodynamics, i.e. genes encoding metabolic enzymes, ion channels and certain neurotransmitter receptors that are targets for AEDs. (Depondt, 2006, Löscher and Schmidt 2011). Several subsequent studies support this theory despite some inconsistencies and poor reproducibility of study findings (Tang et al., 2017).

2.1.7.2.4 Intrinsic severity hypothesis

Intrinsic severity hypothesis suggests that common neurobiological factors are contributing to both epilepsy severity and pharmacoresistance. More severe epilepsy with higher amount of pretreatment seizures would be associated with more refractory epilepsy (Rogawski and Johnson, 2008, Rogawski, 2013). Other study results do not support this theory as the early AED initiation after the first seizures did not affect the future refractoriness (Musicco et al., 1997, Marson et al., 2005).

2.1.7.2.5 Neuronal network hypothesis

In the theory of Fang et al. (2011), seizure-induced degeneration and remodeling of the neural network suppresses the brain's endogenous antiseizure system and restricts AEDs from accessing neuronal targets. Although, alterations in the neural network did not lead to refractoriness in all epilepsy patients. (Fang et al., 2011).

2.1.7.2.6 Pharmacokinetic hypothesis

In this hypothesis, overexpression of drug efflux transporters, such as P-glycoprotein, in peripheral organs are suggested to decrease AED levels in plasma, leading for subtherapeutic AED concentrations in the brain (Lazarowski et al., 2007). This theory has not been validated due to contradicting results and due to the ability for monitoring AED plasma concentrations (Tang et al., 2017).

2.1.7.2.7 Lack of adequate drugs

Some of the epileptogenic mechanisms are not targeted by the current antiepileptic drugs, such as electrical coupling through gap junctions, mitochondrial dysfunction, and autoantibodies to neurotransmitter receptors. This factor presents potential targets for future drug development. The current antiepileptic drugs may not be targeting the appropriate pathogenic processes in some patients as they are intended only to prevent seizures. For example, the patients identified with autoantibodies to ion channels involved in neuronal excitation and inhibition, do not have a response to conventional antiepileptic drugs. (Kwan et al., 2011).

2.1.8 SUDEP

2.1.8.1 Overview

Sudden unexpected death in epilepsy (SUDEP) is a severe, mainly nocturnal phenomenon in epilepsy that is still not fully understood. According to the definition, the death does require witnessing or presence of a seizure, and it is not related to a status epilepticus episode, drowning or trauma. If there is a concurrent non-epilepsy related condition identified at the time of death, it is considered as SUDEP plus incident. (Devinsky et al., 2016, Ali et al., 2017).

SUDEP is the most common cause of epilepsy-related death; up to 50% of the patients with refractory epilepsy and 7-17% of all patients with epilepsy die of SUDEP (Monté et al., 2007).

Basing to the data of 880 cases, 69.3% of SUDEPs occurred during sleep and 30.7% occurred during wakefulness (Ali et al., 2017). As SUDEP is considered a nocturnal phenomenon, sudden cardiac deaths (SCD) have long known to be more

prominent in the early morning hours between 7 AM and 11 AM (Muller et al., 1987). The risk of SCD among patients with epilepsy is 3-fold when compared to the general population, particularly in young women (Bardai et al., 2012). A recent review provides evidence that SCD may constitute an underrecognized cause of death in patients with refractory epilepsy (Verrier et al., 2020).

2.1.8.2 Mechanisms

The knowledge of the mechanisms of SUDEP is limited to a few cases of monitored SUDEPs in humans and some animal experiments. Typically, SUDEP is a nocturnal postictal apnea combined with bradycardia progressing to asystole and death, and it's more likely to occur after a generalized tonic-clonic seizures. Underlying autonomic dysfunction might play a role in the pathophysiology of SUDEP. Brainstem dysfunction associated with postictal EEG suppression has also been identified as a crucial factor. There might also be some relation to dysfunction in serotonin and adenosine signaling systems and genetic disorders affecting cardiac conduction and neuronal excitability (Devinsky et al., 2016, Barot and Nei, 2018, Ryvlin et al., 2019).

2.1.8.3 Risk factors

Although SUDEP, by the definition, cannot be expected, the possible predictive factors and inventories have been studied , but the results have been modest (Monté et al., 2017, Ryvlin et al., 2019). Some SUDEP risk factor have been identified, such as interictal HRV, peri-ictal cardiorespiratory dysfunction and postictal generalized EEG suppression. Later, contradicting results have diminished the role of these factors, and some results suggest that brainstem and thalamic atrophy might be associated with a higher risk of SUDEP (Ryvlin et al., 2019). There is also some evidence of genetic factors increasing the risk for SUDEP (Devinsky et al., 2016).

The SUDEP-7 inventory was developed as a marker of clinical SUDEP risk (Novak et al., 2015). The weighted inventory involves seven parameters for seizure frequency, severity, duration of epilepsy, amount of used AEDs and status of intellectual ability.

Odom and Bateman (2018) compared the SUDEP-7 scores and ILAE risk factors between 16 patients dying of SUDEP and 48 matched patients with epilepsy. The results were not significant reflecting the unpredictable nature of SUDEP.

The risk of SUDEP has been demonstrated to decrease over time in several cohorts. Also, nocturnal supervision and usage of nocturnal listening device appear to be protective. (Ryvlin et al., 2019).

2.1.9 Treatment options

2.1.9.1 Antiepileptic drugs

The first antiepileptic drug, potassium bromide, was introduced over 150 years ago. For a long time, there were not really decent AEDs with good efficacy and tolerable side effects. The advancement has been favorable in that field lately - as shown in Figure 3, there are already up to 40 different antiepileptic drug options, with better efficacy and with lesser side effects. (Schmidt et al., 2014).

The mechanisms of all of the antiepileptic drugs are still not fully understood. The AEDs are grouped according to their main mechanisms of action in Table 2. The sodium channel blockers prevent the channels to return to the active state, therefore preventing the repetitive firing of the axons. The calcium channels play a role in normal rhythmic brain activity, and T-calcium channels are proved to be an important factor of absence seizures. The GABA system can be affected in several ways. The GABA enhancers cause an increment in cell negativity, therefore making it harder to reach an action potential. Some AEDs are antagonists to glutamate, preventing the excitatory effect of glutamate. The glutamate receptor has 5 different binding sites, and different AEDs bind to different parts of it. Some AEDs also inhibit carbonic anhydrase enzyme (e.g. acetazolamide, topiramate, and zonisamide). The intracellular pH decreases, causing potassium ions to shift to the extracellular space resulting in cell hyperpolarization. While estrogen is proconvulsant, progesterone is a natural anticonvulsant with several different mechanisms. Also in some patients, the seizures are highly associated with menstruation, the menstrual cycle could be stopped with progesterone. SV2A (synaptic vesicle protein 2A) binding agents result in decreased action potential-dependent neurotransmission. (Ochoa et al., 2017).

There are several factors to be considered in the choosing of the antiepileptic drug. Some of the medicines have a better effect on certain seizures, leading to a tendency to prescribe certain drugs to specific epilepsies, e.g. lacosamide for focal seizures and valproate for absence seizures. The approved indications for antiepileptic drugs are listed in Table 3 with a preferred first-line option. Along with

the type of epilepsy, one should also pay attention to the other medication of the patient; antiepileptic drugs have a big influence on the metabolic of the other medicines, e.g. carbamazepine inducing cytochrome P450 system, therefore, for example, lowering the plasma concentration of lamotrigine. Some of the drugs require blood sample monitoring, might cause hypersensitivity or be teratogenic. (Schmidt et al., 2014).

Figure 3. History of antiepileptic drugs. The number of antiepileptic drugs on the y-axis and time on the x-axis.

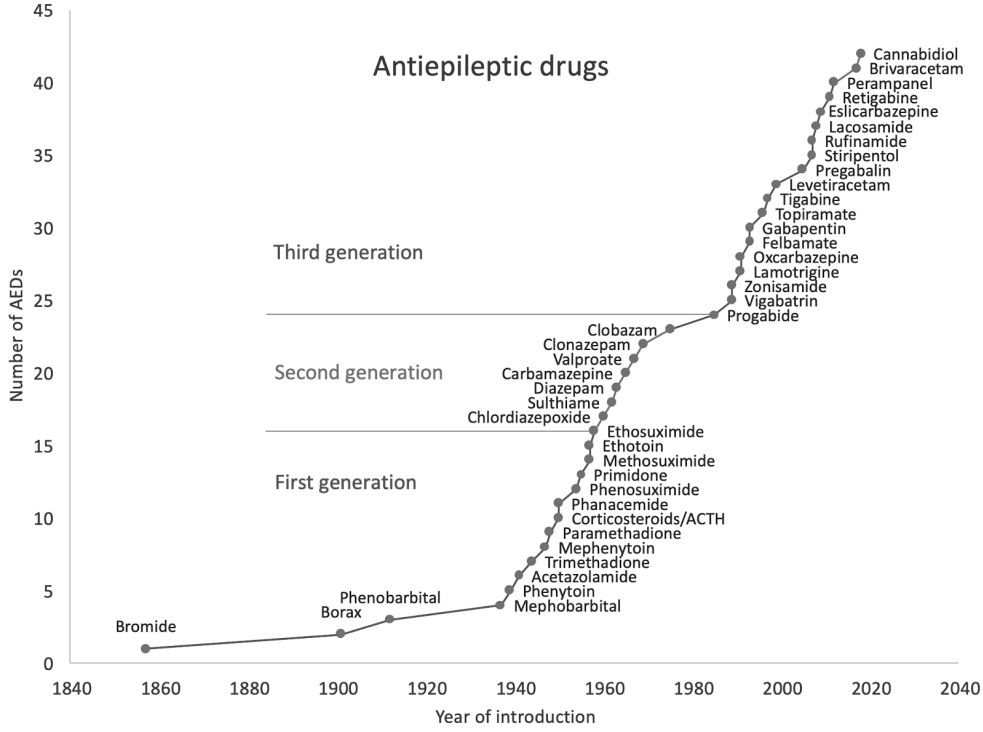


Table 2. Presumed main mechanisms of actions of antiepileptic drugs. Modified from Schmidt et al. (2014).

GABA potentiation	Na+ channel blocker
Potassium bromide Phenobarbital Primidone Diazepam Clonazepam Clobazam Vigabatrin	Phenytoin Carbamazepine Lamotrigine Oxcarbazepine Rufinamide Eslicarbazepine acetate
T-type Ca2+ channel blocker	**Ca2+ blocker (α2δ subunit)**
Ethosuximide	Gabapentin Pregabalin
Multiple	**Other**
Valproate - GABA potentiation, glutamate (NMDA) inhibition, sodium channel, and T-type calcium channel blockade Topiramate - GABA potentiation, glutamate (AMPA) inhibition, sodium, and calcium channel blockade Stiripentol - GABA potentiation, Na+ channel blocker Zonisamide - Na+ channel and T-type calcium channel blocker	Levetiracetam - SV2A (synaptic vesicle protein) modulation Lacosamide - Enhanced slow inactivation of voltage-gated Na+ channels Perampanel - Glutamate (AMPA) antagonist

Table 3. Approved indications for AEDs by Finnish Current Care Guidelines. (Epilepsies (Adults): Current Care Guidelines, 2020). Asterisk (*) refers for a first-line AED.

Focal seizures	Adjunct medications for focal seizures
*Oxcarbazepine *Carbamazepine *Levetiracetam Eslicarbazepine acetate Lacosamide Lamotrigine Topiramate Valproate Gabapentin Zonisamide	Bricaracetam Eslicarbazepine acetate Gabapentin Clobazam Lacosamide Lamotrigine Levetiracetam Perampanel Tiagabine Topiramate Zonisamide Possible alternatives: phenytoin, phenobarbitral, retigabine and vigabatrin.
Generalized seizures	Adjunct medications for generalized seizures
*Valproate Lamotrigine Levetiracetam Topramate	Clobazam Perampanel Zonisamide
Adolescent absence epilepsy	Adjunct medications for adolescent absence epilepsy
*Valproate *Ethosuximide Lamotrigine	Lamotrigine Topiramate Levetiracetam Clobazam Perampanel
Juvenile myoclonic epilepsy	Adjunct medications for myoclonic epilepsy
*Valproate Topiramate Levetiracetam	Perampanel Lamotrigine for FBTCS
Progressive myoclonus epilepsy (Unverricht-Lunborg disease)	Childhood epilepsy syndromes
*Valprotate *Clonazepam or clobazam Adjunct medications: levetiracetam, brivaracetam, perampanel, topiramate, zonisamide, piracetam.	Depending on the syndrome. Non-conventional AED options: Lennox-Gastaut syndrome: rufinamide Dravet syndrome: stripentol Cannabidiol

2.1.9.2 Epilepsy surgery

Some of the refractory focal epilepsies might be treated with epilepsy surgery, although this treatment option is highly underutilized. The epilepsy surgery options can be divided in three main groups; resective surgery, nonresective surgery and disconnection procedures. (Englot et al., 2014, Englot et al., 2017).

The principle of resective surgery is to remove the epileptogenic zone from the brain, usually with a curative goal. The response rate to resective surgery is good, leading to seizure freedom in approximately two-thirds of patients with refractory mesial temporal lobe epilepsy and about one-half of patients with focal neocortical epilepsy in long-term follow-up. The most important predictive factors of the response are early operative intervention, radicality of the resection, and characteristics of the lesion. (Englot et al., 2014, Ryvlin and Rheims, 2016, Engel, 2018).

Nonresective surgery options also include palliative neuromodulation therapies. The recent options for ablative procedures include for example stereotactic laser ablation and stereotactic radiosurgery that are especially effective in patients with mesial temporal lobe epilepsy. These procedures are minimally invasive compared to open surgery with relatively favorable outcomes. The laser ablation of mesial temporal lobe is equal to the resection as a procedure. (Englot et al., 2017).

Disconnection procedures form the last group of epilepsy surgery options, hemispherotomy being the mostly utilized procedure usually with favorable outcome. Corpus callosotomy is a palliative option for patients with intractable atonic seizures and multiple subpial transections would be a possible option for patients with epileptogenic zone within eloquent cortex, although this option is very marginal. Overall, as the nonresective surgery options do not replace the need for resection, they might be a considerable option particularly for the patients who are not amenable for resection or who did not get a satisfying response from the resective surgery. (Ryvlin et al., 2014, Englot et al., 2017, Englot, 2018).

2.1.9.3 Neuromodulation

Neuromodulation therapies, including vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation, are promising palliative nonresective epilepsy surgery treatment options for refractory epilepsy patients not amenable for epilepsy surgery, or after epilepsy surgery with an unsatisfactory response. The VNS and DBS are accounted for in their own chapters.

2.1.9.4 Ketogenic diet

The ketogenic diet (KD) is a dietary program with high fat, low carbohydrate, and adequate protein intake. It was developed in the early 1920s and is being used widely worldwide. The diet is an established option for children with intractable epilepsy, but also a reasonable option for adults with intractable epilepsy that are not candidates for epilepsy surgery, especially in some specific metabolic conditions and in some epileptic syndromes. (Sampaio et al., 2016, Elia et al., 2017).

The mechanism of action is unclear - it might involve alterations in mitochondrial function, effects of ketone bodies on neuronal function and neurotransmitter release, antiepileptic effects of fatty acids, and/or glucose stabilization. (Sampaio et al., 2016). A Cochrane article of KD was published in 2018, but they failed to conduct a meta-analysis due to the heterogeneity and low quality of the evidence of the RCTs published. The reported seizure-freedom and seizure reduction rates were 55% and 85%, correspondingly, in classical KD after three months. In modified Atkins diet (MAD) group, reported seizure-freedom and seizure reduction rates were 25% and 60%, correspondingly, in children. In adults, in the results to one study, seizure reduction rate with MAD was 35%. (Martin-McGill et al., 2018).

The short-term side effects can be acidosis, hypoglycemia, vomiting, obstipation, diarrhea, and gastroesophageal reflux. The long-term side effects, taking place after three months, can be hyperlipidemia, constipation, renal calculi, growth failure, bone health, and deficits of vitamins, minerals and trace elements. (Freeman et al., 2010).

2.1.10 Rhythmicity of epileptic seizures

2.1.10.1 Overview

Clinical experience and several study results show individual patterns in seizure frequencies. Assessed rhythmicity offers a way to modify the treatment of epilepsy; chronotherapy (individual timing of medication) could increase the efficacy and decrease the side effects of AEDs, and prediction of seizures could improve the quality of life of epilepsy patients. Moreover, in novel neuromodulation devices, the stimulation settings could be programmed in circadian rhythmicity to increase and decrease the amount and intensity of stimulations when necessary.

There is evidence of strong circadian variation in epilepsy, epileptiform occurrence peaking nocturnally. Present findings support epileptic seizures

occurring in 24-h, circadian, and sleep-wake- related patterns. Studies have also shown ultradian (most commonly 20-30 days) rhythmicity, the increase in seizure probability being likely related to cortical excitability. (Khan et al., 2018).

2.1.10.2 Rhythmicity regarding to epilepsy and seizure types

Some of the seizures have different patterns based on the epileptic locus. Seizures arising from neocortical regions seem to have a monophasic, nocturnally dominant rhythm. Seizures onsetting in limbic regions have a more complex pattern and diurnal peak. There is also individual variation in the rhythmicity, which is sometimes presented best with a dual oscillator model including circadian and ultradian variations. (Spencer et al., 2016).

The circadian rhythmicity is more common in the temporal epilepsy patients, seizures occurring predominantly in the afternoon or evening (Pavlova et al., 2004, Nzwalo et al., 2016, Quigg et al., 1998), in some results, forming another peak in the morning (Nzwalo et al., 2016). There is some evidence of a peak in seizure occurrence in the evening in extratemporal lobe seizures (Pavlova et al., 2004), but other studies failed in showing any circadian patterns (Quigg et al., 1998, Nzwalo et al., 2016). Frontal lobe seizures typically arise from NREM sleep (Pavlova et al., 2004, Herman et al., 2001).

In children, there are some differences in the patterns. In TLEs, there is evidence of minor increase in seizure frequency during night (Loddenkemper et al., 2011), in results of Ramgopal et al. (2014), TLE seizures occurred mostly during the wakefulness. FLE seizures are more common during night (Loddenkemper et al., 2011, Ramgopal et al., 2014), but in the results of Ramgopal et al., in infants FLE seizures occur more during wakefulness. Zarowski et al. (2011) suggest of seizure circadian patterns for different seizure types in children.

2.1.10.3 Mechanisms

The mechanisms causing circadian patterns in seizure occurrence remain unclear, although the correlation with sleep-wake cycle seems to be the most obvious factor (Khan et al., 2018).

Association between circadian seizure occurrence patterns and the suprachiasmatic nuclei (SCN) in the anterior hypothalamus has been suspected due to the circadian expression of certain genes and their feedback systems, and due to

the projections from SCN to epileptic networks (Loddenkemper et al., 2011, Khan et al., 2018).

Cortical excitability is proposed to vary in regard of the time of the day and after a sleep deprivation (Ly et al., 2016). Also, sleep-related oscillative thalamo-cortical circuits and altered function in several thalamic neurons might have effect on generating seizures (Beenhakker and Huguenard, 2009).

There is some evidence that circadian rhythmicity of seizures is induced by the hormonal system, especially by the stress hormones. Stress is a known precipitant of seizures; stress hormones such as cortisol affect neuronal excitability and seizure threshold. The similarities between the circadian rhythmicity of seizures and the release of cortisol were evaluated in a systematic review. Both seizure occurrence and cortisol concentration showed similar circadian patterns; a sharp rise in the early morning with a following gradual decline, particularly in generalized and focal parietal lobe onset seizures (van Campen et al., 2015). The effect of stress hormones on higher seizure occurrence is proposed to be mediated through fast non-genomic and slow gene-mediated pathways in several structures within hippocampal circuits (Goodman et al., 2019, Gunn and Baram, 2017).

Along with cortisol, other hormones and compounds, such as melatonin, serotonin, and adenosine, might affect seizure occurrence (Loddenkemper et al., 2011). Nocturnal activation of melatonin receptors during darkness suppresses hippocampal $GABA_A$ receptors in rodents (Stewart and Leung, 2005), leading to more excitable temporal lobe during the night. There is also some evidence of decreased seizure occurrence during bright days (Baxendale, 2009). Association between menstrual cycle and seizure occurrence is established (Ochoa et al., 2017).

2.1.11 Predicting seizures

Reliable biomarkers to predict epileptic seizures have been tried to discover.

Some patients experience prodromal symptoms, and functional MRI and near-infrared spectroscopy have shown perfusion increasing before the seizures. Transcranial magnetic stimulation experiments have shown the brain being in a hyperexcitable state before the seizures, hyperexcitability also being shown in auditory and visual steady-state responses along with the direct electrical stimulation as a precursor of epileptic seizures. There is also a seizure advisory system that analyzes EEG in real-time by recording the brain activity intracranially, and giving a

signal of emerging seizure to help the patients to get the treatment even before the clinical seizure starts. (Cook et al., 2013).

Interictal spikes in EEG, according to one hypothesis, are a consequence of increased neural excitability, possibly leading to a seizure. Another hypothesis proposes that the spikes might also have beneficial effects regarding the seizures as the spikes are often followed by a period of hyperpolarization, which may limit the interictal activity and regulate the propagation of a seizure. In one study, nine out of 15 patients experienced a significant change in the spike rate prior to seizures. Within six of them, the spike rate was decreased. (Karoly et al., 2016).

Monitoring the heart rate of the patient is one possibility of predicting emerging seizures in some patients (see chapter 2.2.6).

2.1.12 Detecting seizures

Along with EEG monitoring, several non-EEG based methods for detecting seizures have been investigated.

Cardiac manifestations of seizures are useful and relatively reliable procedures to detect emerging or ongoing seizures. It has been assessed for long, that seizures are capable of causing alterations in cardiac functions. Behbahani et al. (2013) brought up the idea of finding an algorithm basing on the autonomic control of the heart, in order to find a way to detect emerging seizures. They found significant changes in HRV on the pre-ictal phase compared to the interictal phase. Osorio et al. (2015) assessed if various biological factors alter the probability to detect the seizures reliably. The probability seems to be higher in males with longer duration of epilepsy, not being related to the hemisphere of origin and it was most efficient to detect focal impaired awareness seizures.

There are several different algorithms to assess HRV with different accuracies. Jeppesen et al. (2015) compared four different algorithms and found variety in detecting seizures, and also in distinguishing seizures from physiological heart rate changes during exercise. Pavei et al. (2017) tested the false positive (FP) rates of the seizure detection system with epilepsy patients and with a healthy control group. In the group of epilepsy patients, the sensitivity was 94.1% and FP rate $0.49h^{-1}$, whereas the FP rate with healthy subjects was $0.19h^{-1}$.

There are several wearable seizure-detection devices available, and there is a lot of development work of new devices in that field. The non-EEG based wearable seizure detection devices monitor patients' heart rate, arterial oxygenation,

accelerometry, electrodermal activity, and temperature. By discovering a pattern between these monitorable factors and seizures, it might be possible to predict seizures. Cogan et al. (2015) studied the wrist-worn biosensors finding a pattern of increased heart rate, an alteration in arterial oxygenation, following altered electrodermal activity, and they are currently studying it further to develop more reliable seizure-detecting devices, with fairly promising results (Cogan et al., 2017). Vandecasteele et al. (2017) compared the hospital ECG system with a seizure predicting algorithm to the wearable ECG- and PPG (photoplethysmography) systems. The sensitivity and false alarms per hour for the hospital system were 57% and 1.92, for wearable ECG system 70% and 2.11, and for the wearable PPG system 32% and 1.80, suggesting the wearable ECG system functioning relatively well.

2.2 VNS therapy

2.2.1 Relevant physiology

2.2.1.1 Vagus nerve

2.2.1.1.1 Anatomy

The vagus nerve *(nervus vagus)* is a bilateral, tenth cranial nerve. In its entirety, the vagus nerve forms an extensive afferent and efferent network spreading around the human body more widely than any other cranial nerve; neck, thorax, and abdomen, having influence over cardiac and digestive functions, connecting the central nervous system (CNS) to the rest of the body. The vagus nerve contains different types of fibers; approximately 80% of them are sensory afferent and 20% of them are motor efferent fibers.

The vagus nerve originates as a group of rootlets on the anterolateral surface of the medulla oblongata just below the ninth cranial nerve, glossopharyngeal nerve. The rootlets enter to the jugular foramen. While and after passing through the foramen, the rootlets merge to form the vagus nerve. At the foramen, or immediately after it, there are two ganglia, the superior (jugular) and inferior (nodose) ganglia, that contain the cell bodies of the sensory neurons of the vagus nerve. (Drake et al., 2010).

Vagus nerve fibers can be classified into A, B, and C groups, and their subgroups. The vagus nerve consists of approximately 80% of C-fibers and 20% of A- and B-fibers. The A-group consists of myelinated, somatic, afferent, and efferent fibers with a diameter of 1 to 22 μm and a conduction velocity of 5 to 120m/s. The B-fibers are moderately myelinated, efferent, and mainly preganglionic autonomic fibers with a diameter of ≤ 3 μm and a conduction velocity of 3 to 15 m/s. The C-fibers are afferent and unmyelinated. (Helmers et al., 2012)

2.2.1.1.2 Innervation

The innervation of the vagus nerve to its whole extent is still not fully known. The different fiber types with their innervation are roughly explained below. (Drake et al., 2010).

General Somatic Afferent (GSA) fibers: larynx, laryngopharynx, deeper parts of the auricle, part of the external acoustic meatus and the dura mater in the posterior cranial fossa.

General Visceral Afferent (GVA) fibers: aortic body chemoreceptors, aortic arch baroreceptors, esophagus, bronchi, lungs, heart, and abdominal viscera in the foregut and midgut.

Special Afferent (SA) fibers: taste around the epiglottis.

General Visceral Efferent (GVE) fibers: part of the parasympathetic part of the autonomic peripheral nervous system stimulating smooth muscle and glands in the pharynx, larynx, thoracic viscera, and abdominal viscera of the foregut and midgut.

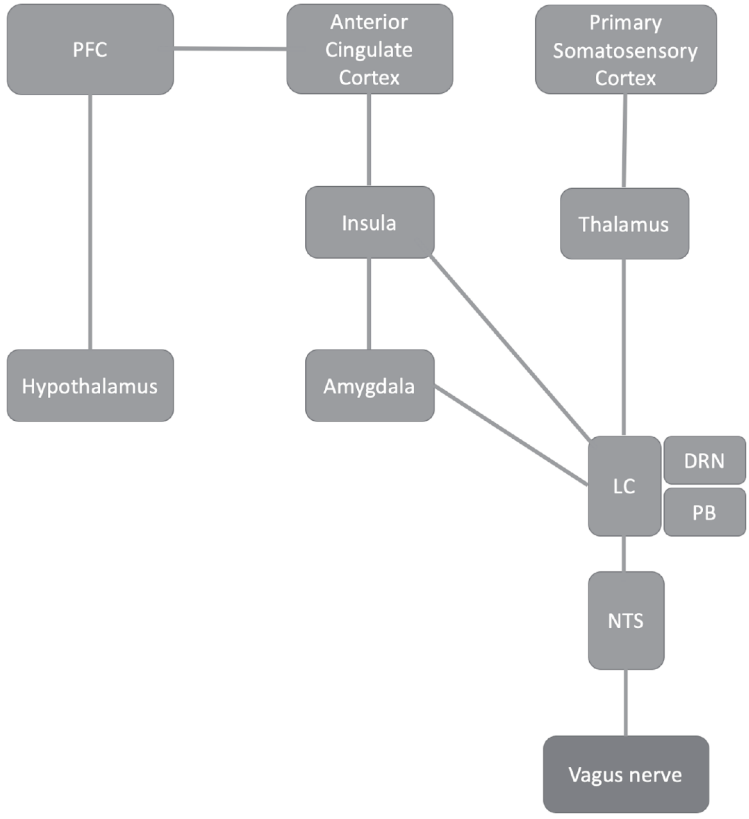
Branchial Efferent (BE) fibers: motor functions of the tongue (palatoglossus), soft palate (except tensor veli palatini), pharynx (except stylopharyngeus) and larynx.

In the medulla oblongata, there are four nuclei affiliating with the vagus nerve. The *dorsal nucleus of the vagus nerve* sends parasympathetic output to the viscera. *Nucleus ambiguus* is the origin of the BE fibers and preganglionic parasympathetic neurons innervating the heart. *Solitary nucleus* receives afferent taste information and primary afferents from visceral organs, and the *spinal trigeminal nucleus* receives information about deep touch, pain, and temperature of the outer ear, the dura of the posterior cranial fossa and the mucosa of the larynx.

2.2.1.1.3 The Vagus Afferent Network

The anatomical neural pathway, "vagus afferent network", is explained in this chapter, visually presented in Figure 4. The functional consequences of vagal stimulation in the brain are discussed further in the chapter 2.2.5. (Hachem et al., 2018).

Figure 4. The Vagus Afferent Network. NTS = nucleus tractus solitarius, LC = locus coeruleus, DRN = dorsal raphe nucleus, PB = parabrachial nucleus. (Modified from Hachem et al., 2018).



Afferent vagal fibers mainly project to the nucleus tractus solitarius (NTS), which sends fibers to other brainstem nuclei important in modulating the activity of subcortical and cortical circuitry.

NTS receives direct input from the vagus nerve, channeling the inputs to other brainstem nuclei including the locus coeruleus (LC), dorsal raphe nucleus (DRN), and parabrachial nucleus (PBN) along with forebrain limbic structures. LC is a

noradrenergic nucleus that receives direct inputs from NTS and projects widely to limbic structures.

DRN is a serotonergic nucleus, possibly receiving inputs from NTS. However, there seem to be indirect projections from the LC to the DRN, which again sends widespread connections to upper cortical regions.

PBN also gets innervation from vagal afferents. Then PBN's upstream cholinergic pathways send diffuse outputs to forebrain structures including the thalamus, insular cortex, amygdala, and hypothalamus. Supposedly, PBN has an important role in regulating thalamocortical circuitry that may have a relation to seizure generation.

2.2.1.2 Hypothalamic-Pituitary-Adrenal axis

The hypothalamic-pituitary-adrenal axis (HPA axis) is a major neuroendocrine pathway leading to the secretion of the hormones that control autonomic functions all over the body. One of the important objectives of the HPA axis is the secretion of cortisol, an essential stress hormone, from adrenal glands. (Guyton and Hall, 2011). In the brain, the effects of cortisol are mediated through two pathways; fast non-genomic and slow gene-mediated neuronal actions. The increase of cortisol concentration leads to increased attention and vigilance, as well as areas involved in emotional responses, and simple behavioral strategies are showing enhanced activity. These concurrent activities most likely help the individual to link the stressful event to higher cognitive functions to learn to cope in such a situation. (Joëls, 2018).

The secretion of cortisol simplified, the hypothalamus secretes a hormone called corticotropin-releasing hormone (CRH), which in turn leads to the secretion of ACTH (adrenocorticotropic hormone) in the anterior lobe of the pituitary gland, which again leads to the secretion of cortisol hormone. Along with this pathway, the hypothalamus and pituitary glands secrete a variety of different hormones affecting the whole body. The system is regulated through humoral and neural feedback systems. (Guyton and Hall, 2011).

Cortisol secretion is also increased during the time of morning wake-up, also known as cortisol awakening response (CAR). Awakening activates the HPA axis, which mostly induces the cortisol secretion, and is fine-tuned by direct sympathetic input to the adrenal gland modulating its ACTH sensitivity. Simultaneously the cardiovascular system activates due to awakening shifting the autonomic nervous system towards sympathetic dominance. CAR seems to be related to heart rate and heart rate variability but not to the cardiac autonomic activation. (Stadler et al., 2011).

2.2.1.3 Autonomic dysfunction

Autonomic dysfunction is often associated with epilepsy, and the alterations monitored by cardiac functions can be found during and between the seizures. The autonomic dysfunction is proposed to be involved in epilepsy pathogenesis along with the risk of SUDEP (sudden unexpected death in epilepsy).

Diehl et al. (1997) investigated alterations in cerebral artery blood flow velocities and suggested of an increased sympathetic activity in the patients with epilepsy even in the absence of seizures.

Heart rate variability (HRV) is the fluctuation in the time between the heartbeats. The ability of the heart to suddenly faster or slower the rhythm is an essential factor maintaining the homeostasis during sudden physical and psychological events. HRV can be used as a reflector of the autonomic functions of a body. As the rapid changes in HRV are usually mediated by the autonomic nervous system, humoral factors affect the HRV more slowly. (Shaffer et al., 2017). Patients with epilepsy tend to have reduced HRV reflecting the autonomic dysfunction on the sympathetic dominance (Tomson et al., 1998, Ronkainen et al., 2005, Harnod et al., 2009, Mukherjee et al., 2009, Hirfanoglu et al., 2018, Yuan et al., 2017).

Along with the HRV, T-Wave Alternans (TWA) is another cardiac biomarker reflecting the function of the autonomic nervous system. It is an established biomarker of cardiac mortality in patients with heart disease (Verrier et al., 2011). TWA is also known to be elevated in patients with refractory epilepsy (Strzelczyk et al., 2011), and to be significantly higher with chronic epilepsy than in newly diagnosed patients (Pang et al., 2019).

There is some evidence of an association between SUDEP and autonomic dysfunction. Nei et al. (2004) found evidence of increased autonomic activity (measured by heart rate) associated with seizures especially during sleep in patients that later died of SUDEP. Picard et al. (2017) back this hypothesis up with their case-report of a patient - they propose autonomic dysfunction (simultaneous sympathetic and parasympathetic hyperactivity) and postictal cerebral dysfunction to be important mechanisms behind SUDEP. Also, Poh et al. (2012) investigated the autonomic dysregulation associating with SUDEP; the duration of postictal EEG suppression correlates with sympathetic activation and parasympathetic suppression. These findings were more severe with generalized tonic-clonic seizures than focal impaired awareness seizures. Myers et al. (2018) assessed the role of autonomic dysregulation in association with SUDEP in sodium channel (SCN) gene mutation patients. In their material the association between SUDEP and autonomic

dysfunction measured by HRV was obvious, the dysfunction was slightly worse in SCN patients.

2.2.2 History of VNS

First experiments of stimulation of the vagus nerve were conducted in the late 1980. Before initiating the in-human experiments with VNS, vagal stimulation was first experimented with animals in several studies. Before focusing on the seizures, Zabara (1988) experimented with the effect of vagal stimulation on drug-induced emesis in cats. Woodbury et al. (1990) reported that stimulation of vagal C fibers in young male rats prevents or reduces chemically and electrically induced seizures. Lockard et al. (1990) reported promising results in monkeys, whereas two out of four monkeys became seizure-free. Zabara (1992) found that chemically induced seizures in dogs were terminated with vagal nerve stimulation within 5 seconds. Furthermore, the data of this study also supported the hypothesis that the antiseizure effect is derived via small-diameter unmyelinated fibers in the vagus nerve.

The first time the vagal nerve was electrically stimulated in humans, was in the United States in 1988. The patients tolerated the stimulation well, but because of the short follow-up time (6-12 months), the results regarding the seizure frequency were not conclusive (Penry et al., 1990). Michael et al. (1993) first reported the anticonvulsant effect of VNS. Of the cohort of 15 patients, six (40%) obtained at least a 50% reduction in seizure frequency.

After the first introduction of VNS, several studies were conducted showing its potential efficacy. VNS therapy received the European approval in 1994. In the United States, VNS was approved as a treatment option for medically refractory partial-onset seizures in adults and adolescents in 1997 by the FDA (US Food and Drug Administration). By the end of March 2020, worldwide more than 120 000 patients, including 30 000 children, have received VNS therapy (LivaNova, 2020).

2.2.3 Indications

Patients with refractory epilepsy comprise approximately 30% of all patients with epilepsy (Kwan and Brodie, 2000). For this patient group, resective surgery would be the treatment of choice, but the majority of patients are not amenable for the epilepsy surgery (Cloppenborg et al., 2016). Possibilities for major improvement with

antiepileptic drug (AED) therapy are limited, therefore neurostimulation therapies are a necessary addition for the treatment options.

The indications for VNS therapy in patients with refractory epilepsy are the following (Giordano et al., 2017, Yamamoto, 2015):

- Focal epilepsy with multiple and bilateral independent foci.
- Patients with diffuse epileptogenic abnormalities.
- Refractory IGE (idiopathic generalized epilepsy).
- Seizures persist after epilepsy surgery.
- Epilepsy surgery is contraindicated.

2.2.4 VNS surgery

The original description of implantation by Reid (1990) is still valid and standardized implantation technique. The following description of implantation is summarized from the article of Giordano et al. (2017).

The VNS kit includes a titanium-housed pulse generator with battery, a lead wire with two helical electrodes, and a helical tethering anchor, and a tunneler.

First, a 3-4 cm transverse skin incision is made in a skin fold to the left neck, roughly halfway between the mastoid and the clavicle. The incision is extended through the platysma muscle and the fascial plate, and the carotid sheath is identified medially to the internal jugular vein. The operation is continued using the operating microscope or the surgical loops. The vagus nerve is identified and bluntly dissected for a length of 3-4 cm, avoiding any excessive damage. The tethering anchor, positive and the negative electrodes (inferior, middle, and superior correspondingly) are positioned around the nerve, inferior to the cardiac branches to avoid cardiac side effects. After implanting the electrodes, the function of the device is checked by temporarily connecting the battery to the lead electrode to test the lead impedance by a single stimulation impulse. A high impedance (> 1 700 – 2 000Ω) means, that the electrodes are not in good contact with the nerve and should be checked and fixed.

Then the subcutaneous pocket is bluntly made, 5 cm in length and height. Either 5 cm below the clavicle, or just medial to the axilla and superior to the breast. The stimulator lead is positioned by using the tunneler. A strain relief bend is made to the lead to provide slack during future movements of the neck. After that, the electrode is secured in two points by suturing silicon head holders. The battery is

fixed to the lead electrode and anchored by sutures. Finally, the two wounds are sutured in anatomical layers.

The patients usually stay at the hospital until the next day and the position of the device is checked with X-ray.

2.2.5 Principle & mechanism of action

2.2.5.1 The principle of the action of VNS

The main principle of VNS is to deliver electrical current to the brain in order to reach beneficial effects on specific diseases. The pacemaker-like pulse generator implanted to the upper chest generates the electrical current which is delivered to the brain via 10th cranial nerve, *n. vagus*. The US Food and Drug Administration (FDA) has approved VNS for the treatment of epilepsy, depression, and obesity. The mechanisms causing the effects are not fully understood; current hypotheses are described below.

The programmable settings of the VNS device in normal mode stimulation are output current (I, mA), pulse width (Pw, μs), pulse frequency (f, Hz), ON-time (t_{ON}, s) and OFF-time (t_{OFF}, min).

The number of nerve fibers recruited by the stimulation is dependent on the output current. Almost all the fibers in the vagus nerve are activated already with the current of 1.5mA (Helmers et al., 2012). First, the large A fibers are activated associating with the recurrent laryngeal nerve, without having an effect on seizures. Next, the fast B fibers are recruited and have been suggested that the B fibers are the source of efficacy in treating seizures as having projections to several areas in the brain via nucleus of the solitary tract. When the current is further increased, adverse effects e.g. coughing may occur, possibly due to the recruitment of smaller and deeper pulmonary fibers. (Arle et al., 2016).

Controversially to the initial hypothesis, the small and unmyelinated C-fibers are not believed to be involved in the anticonvulsive effects of VNS (Krahl et al., 2001).

2.2.5.2 The mechanism of action: hypotheses

VNS is proposed to have three different mechanisms of action:

i) immediate termination of a seizure (McLachlan, 1993),

ii) short term anticonvulsive effect of stimulation (Takaya et al., 1996),
iii) long term effects on neural circuitries (Naritoku et al., 1995).

Cyclic stimulation (normal mode) has major effects via the two latter mechanisms whereas magnet mode is applied to stop the seizures. Due to multiple reasons, usage of the magnet is not always possible during the seizure, e.g. patients could lose the ability to operate, not recognize the emerging seizures, or could be asleep. The latest models of VNS (106 AspireSR and newer) also provide automatic detection of seizures (closed-loop VNS or responsive VNS, rVNS). The operating principle of automatic stimulation (AutoStim) is to detect the ongoing or emerging seizure and to produce excessive stimulations when the seizures are detected, along with the normal mode cyclic stimulation. The automatic stimulation is discussed further in chapter 2.2.6.

Of these three effects, the last one, indirect effect, would be achieved after a longer duration of the therapy, while the first two are immediate and direct effects of stimulation. The efficacy might also be associated with modifications of neural pathways, the function of the autonomic nervous system, recovery from neuroanatomic lesions and immunomodulatory effects of VNS. A recent study of intracranial responsive neurostimulation concluded that the effects were mediated through long-term modulation of seizure network activities instead of immediate effects of stimulation. (Kokkinos et al., 2019). These findings might apply also for VNS therapy.

The biological mechanisms causing the effects of vagus nerve stimulation are still not fully understood, but there are several hypotheses about the effects, described in detail below. The hypotheses include the release of noradrenaline and serotonin in CNS (central nervous system), immunomodulatory effects of stimulation and the effect on desynchronization of EEG (electroencephalography) and reduction of IEDs (interictal epileptiform discharge).

2.2.5.2.1 Excitation of LC and DRN: the role of norepinephrine and serotonin

The main terminus of the afferent fibers of the vagus nerve is the NTS, which has direct and indirect projections to the LC, raphe nuclei, reticular formation and many other brainstem nuclei (Krahl et al., 2012). VNS excitates both LC and DRN, thus inducing the secretion of extracellular norepinephrine (NE) and serotonin. There are evidence of these neurotransmitters to play prominent roles in seizure suppression.

The LC is known to be an important source of NE in the brain. It has been suggested, that the effects of vagal stimulation on learning and memory, mood, seizure suppression, and recovery of function after brain damage are partly mediated by the release of extracellular NE in the brain (Roosevelt et al., 2006).

Roosevelt et al. (2006) demonstrated with their rat experiment, that electrical stimulation of left vagal nerve increases the concentration of NE in the brain intensity-dependently. Stimulation at 0.0 and 0.25mA did not increase the NE concentration, whereas 0.5 mA stimulation increased the NA concentration in the hippocampus significantly (23%), but not in the cortex. 1.0mA stimulation increased NE concentrations significantly both in the hippocampus (28%) bilaterally and in the cortex (39%), and the NE increase was present only during the stimulus. The stimulation did not alter the NE concentrations between the stimuli and after the stimulation periods.

The first results of the electrical nerve stimulation of LC are from the research of Takigawa et al. (1977). They found out that in rats the majority of LC neurons were transiently inhibited by VNS, following longer excitation phase. The researches of Groves et al. (2005) and Naritoku et al. (1995) also back up the hypothesis of LC being activated by acute VNS. Dorr et al. (2006) compared the acute (1-hour activation) to chronic (up to 90 days) activation. They pointed out that chronic activation has remarkable and prolonged activation of LC neurons, NE-firing rate being doubled compared to the control group. In the same study, they found similar results in DRN activity, which is an important serotonergic nucleus. Acute (less than 3 days) stimulation did not have a significant effect on DRN neurons whereas chronic (more than 14 days) stimulation nearly doubled the DRN activity compared to the baseline. Hulsey et al. (2017) discovered the higher current intensities and longer pulse widths causing greater increases in LC firing rate, however varying the pulse frequency not affecting phasic LC activity.

Krahl et al. (1998) proved LC's position in the effect on the seizures by VNS with rat experiments. They either chronically depleted LC of NE with a bilateral infusion of 6-hydroxydopamine (6-OHDA) into the LC, or LC was inactivated with lidocaine. After two weeks they induced seizures with maximal electroshocks (MES) to assess the VNS-induced seizure suppression. In a control group, the seizure severities were significantly reduced, whereas animals with LC lesion the effect of VNS were dampened. Raedt et al. (2011) induced seizures in rats by infusing pilocarpine into the hippocampi of rats. VNS reduced the seizure severity, but when also α2-adrenoreceptor antagonist was infused into the hippocampus, VNS-induced seizure suppression was abolished. This finding supports the hypothesis of noradrenergic

signaling in the hippocampus acting an important role in the VNS effect of seizure-suppressing.

The evidence concerning seizure suppression through activation of serotonergic neurons in the raphe nuclei is less comprehensive than the evidence concerning the norepinephrine release from the LC. Browning et al. (1997) chemically destroyed the serotonergic neurons with a selective serotonin neurotoxin, followed by the abolished effect of VNS on suppressing chemically induced seizures. Ben-Menachem et al. (1995) found out that VNS caused a 33% increase in 5-HIAA, a serotonin metabolite, in cerebrospinal fluid, proving the VNS-induced serotonergic activity in the brain.

2.2.5.2.2 Effects on EEG desynchronization

VNS is also proven to prevent and stop seizures also directly with the electrical stimulation. The main hypothesis is that electrical stimulation causes EEG desynchronization, leading to anticonvulsive effects. VNS has also a reductive effect on IEDs on EEG.

The first study assessing the VNS effects on human EEG (Koo, 2001) proposes VNS increasing the periods of spike-free intervals and inducing EEG desynchronization over time. In the patient group where seizure frequencies show significant reduction after VNS surgery the desynchronization in the gamma frequency band was statistically decreased when compared to the non-responders over a time span of five years. The other EEG frequencies stood unaffected (Franschini et al., 2013). Patients responding to VNS had a lower level of broadband EEG synchronization than non-responders. It also might be possible to predict response to VNS therapy by estimating changes in the synchronization level. (Bodin et al., 2015). Later they studied the impact of VNS in functional connectivity (Fc) in the brain with five patients and found out that VNS might have impact on the Fc. The effects were variable, either decreased or increased, and were not uniformly distributed but prominent in some anatomical regions. There was an analogy with the Fc alteration and response: the only patient with decreased connectivity was a responder. (Bartolomei et al., 2016).

Wang et al. (2009) conducted a follow-up study with multiple EEG registrations among 8 new VNS initiations. In addition to a progressive seizure reduction, the results included statistically significant progressive decrease in the number of IEDs on EEG.

2.2.5.2.3 Effects on neural networks

It is known that refractory epilepsy affects the ability to organize resting-state networks of the brain. In a study with one patient, Wang et al. (2016) compared the changes in resting-state brain networks analyzed with functional MRI imaging, forming a hypothesis of VNS altering those networks. After 6 months of VNS treatment, they were slightly reorganized; excessive activation of the salience network was suppressed, as at the same time the suppressed default-mode network was activated.

Also, Franschini et al. (2014) studied the effects of VNS on functional brain networks. They used the phase lag index to estimate functional connectivity between EEG channels and the minimum spanning tree was used to characterize changes in the network topology. Within patients responding to VNS, they discovered clear brain network reorganization towards more integrated (more efficient) architecture. They hypothesize that the reorganization of functional brain network might cause the effects of VNS, and that the minimum spanning tree analysis is a useful way to evaluate and to monitor the efficacy of VNS. The alteration in large-scale networks might also explain why VNS affects also mood and psychiatric conditions along with epilepsy.

2.2.5.2.4 Immunomodulatory effects; the role of inflammation in epilepsy pathogenesis

Over the last decade, a large amount of evidence strongly supports the role of inflammation in the pathophysiology of human epilepsy. Specific inflammatory molecules and pathways have been identified in different experimental models of epilepsy and also the same inflammatory pathways have been found in surgically resected brain tissue samples from the patients with refractory epilepsy. These findings offer a novel target in the treatment of epilepsy (Aronica et al., 2017).

VNS has also immunomodulatory effects. First, secreted norepinephrine itself inhibits inflammatory gene expression in glial cells with unclear mechanisms (Gavrilyuk et al., 2002). Second, the stimulation of afferent vagal nerve fibers further activates the efferent nerve fibers targeting the cholinergic anti-inflammatory pathway inhibiting the release of pro-inflammatory cytokines, e.g. tumor necrosis factor-alpha (TNFα) that reduce inflammation (Panebianco et al., 2015, Bonaz et al., 2017). Third, the vagal afferents targeting to HPA axis lead to the secretion of anti-inflammatory hormones such as cortisol (Bonaz et al., 2017). Mediated by the immunomodulatory mechanism, VNS might also have positive effects on behavior,

mood, and cognition, thus offering a promising treatment option also for Alzheimer's disease (Vonck and Raedt, 2014).

2.2.6 Automatic stimulation

VNS therapy consisted earlier of cyclic normal mode and magnetic mode stimulation. The newer models, VNS 106 AspireSR and SenTiva, offer also a new treatment modality: the device monitors a patient's heart rate and according to its algorithm based on heart rate variation, it automatically produces additional stimulations when detecting ictal tachycardia as a sign of an emerging or ongoing seizure. This modality is called automatic stimulation (AutoStim, also known as closed-loop VNS or responsive VNS, rVNS).

The device itself is slightly larger than some other models and due to the heart rate detecting system, the placement is more accurate than with the other models. The implantation procedure and possible complications are the same as with the other VNS models. (Schneider et al., 2015). The manufacturer provides instructions for the preoperational ECG examinations for the determination of the correct heartbeat sensitivity setting according to the amplitudes of R waves. This examination is also possible to fulfill reliably intraoperatively. (Robbins et al., 2017).

The necessity for automatic stimulation originated from the experience with magnet mode stimulation, of which effectivity on seizures has been proven. However, due to several reasons, manual stimulation might not be possible. The patient might be asleep, the magnet might not be on hand when needed or consciousness might be disturbed. Therefore an option for automatized on-demand excessive stimulation for seizures is highly beneficial.

As discussed further in chapter 2.1.11, there are several ways to predict epileptic seizures and a biomarker is needed to automatically trigger the automatic stimulation. Epileptic seizures typically cause an increase in heart rate, and monitoring heart rate does not require more invasive operations than former VNS systems, therefore it is an applicable biomarker for epileptic seizures. The electrodes detecting the heart rate are the case of the pulse generator and one lead electrode.

The ictal tachycardia as a biomarker for epileptic seizures was first proposed as an option for a clinical tool by Zijlmans et al. (2002) and it has been studied subsequently further. According to a review, tachycardia is present on seizure onset in 82% of the patients, and on average in 64% of generalized and in 71% focal onset seizures, especially on temporal lobe seizures (Eggleston et al., 2014). The increasing

effect on heart rate and decreasing effect on heart rate variability (HRV) is especially high in bitemporal seizures (Page et al., 2018). These findings might be related to the association and connections between the autonomic nervous system and the vagal afferent network to the temporal lobes of the brain (Kiernan et al., 2012, Chouchou et al., 2017, Hachem et al., 2018). Moreover, bilateral tonic-clonic seizures often induce greater and longer-lasting tachycardia than focal seizures (Surges et al., 2010). However, also ictal bradycardia or even asystole are possible manifestations of a seizure, even though being rare (Duplyakov et al., 2014). The ictal tachycardia might be the first clinical sign of a seizure. In a study on patients with ictal tachycardia the onset of tachycardia varied from 21.6 to 23.7 seconds after the onset of a ictal EEG changes. With most of the patients (10/13, 76.9%) and most of the seizures (56/78, 71.8%), the ictal tachycardia was detected before any other clinical signs,. (Hirsch et al., 2015).

The proof of a concept was demonstrated in a video-EEG study that showed that the autostimulation was triggered by an epileptic seizure in a substantial part of the seizures and was indeed able to stop some seizures (Hampel et al., 2015), followed by subsequent studies to establish the position of rVNS therapy in the treatment of refractory epilepsy (Boon et al., 2015, Fisher et al., 2016).

The device can be programmed to respond to different levels of increases in the heart rate algorithm, ranging from 20% to 70%. The lower the threshold, the more seizures were detected, maximizing the probability to detect a seizure, with a shorter delay. Emphasizing the sensitivity naturally leads to lesser specificity and causes more false-positive, i.e. non-seizure-related, stimulations. In the E36 trial the patients receiving stimulation with the threshold of 20%, had approximately 7 false-positive stimulations every hour. As a comparison, the patients receiving normal mode stimulation with a therapy time of 10%, 11 stimulations per hour are delivered. (Boon et al., 2015).

However, in addition to stopping the ongoing or emerging seizures, the automatic stimulations also have an effect on two other mechanisms of action, as presented in chapter 2.2.5.2. Autostimulation also changes the profile of the daily stimulation from constant stable cycling to more variable stimulation, which also has been hypothesized to have a beneficial long-term effect on seizure control.

2.2.7 Prognosis

2.2.7.1 Efficacy on seizures

The therapeutic effect of VNS in refractory epilepsy patients has been assessed in several studies. The common presumption is that VNS treatment reduces seizure frequencies ranging from 30% (Ryvlin et al., 2014) to over 50% (Cukiert, 2015), or even more than 60% (Elliott et al., 2011), within at least 50% of the patients with refractory epilepsy. The response improves over time. (Elliott et al., 2011, Englot et al., 2016, Révész et al., 2018, Wang et al., 2019)

Several blinded, randomized controlled trials has been published. The patients are divided in two groups in these trials; receiving either therapeutic, or subtherapeutic levels of stimulation for three months. A "responder" is defined as a 50% reduction or more in seizure count.

In the multicenter study of VNS study group comprising 114 patients, the mean reduction of the seizure frequency was 25% in the stimulation group whereas the reduction in the control group was 6%. Responder rate was 31% and the differences were significant (VNS Study Group, 1995).

Handforth et al. (1998) had 196 patients in their study. Their mean seizure reduction rate was 28% compared to 15% in the control group and the responder rate was 23%, results were significant.

Amar et al. (1998) included in their single-center study only 17 patients and resulted a mean seizure reduction rate as high as 71% compared to 6% with a responder rate of 57%.

Michael et al. (2005) included 10 patients with 12 controls in their multicenter study. Mean seizure reduction was 33.1% compared to 0.6% with a responder rate of 40%, results were significant.

Englot et al. (2016) performed a registry study comprising 5554 patients, also including 2869 patients from a systematic review of the literature. In the registry study, they found a progressive response over time; 49% of patients responded to VNS therapy in 4 months after implantation and 5.1% of the patients achieved seizure freedom. At 24 to 48 months, 63% of patients were responders and 8.2% achieved seizure freedom. The systematic literature review results support this finding: Initially, 40.0% of patients were responders (2.6% were seizure-free), while at the last follow-up point 60.1% of patients were responders (8.0% were seizure-free). Another extensive meta-analysis (Wang et al., 2019) presents similar results with linear improvement: at the time points of 6 months and 12 years after

implantation, 34.0% and 82.9% of the patients were responders. In the cohort of Révész et al. (2018) the responder rate almost doubled between time points of one and five years after the implantation, the largest increase placed between the first and second year of follow-up. Similar trend is also visible in the results of Elliott et al. (2011).

The improved seizure situation could lead to a reduction in antiepileptic drug therapy in dosage and number (Tatum et al., 2001). Since patients with VNS therapy are usually also treated with drugs, it may be difficult to determine if the beneficial effects are due to medication or VNS. Arcand et al. (2017) questioned the effect of VNS on seizures since the AED regimen changes are also performed during VNS therapy in normal clinical practice. They concluded that the VNS is an effective therapy, although the AED therapy naturally also reduces seizures and the real decrease in seizure frequency is impossible to assess reliably if there are alterations in drug therapy. In the study of García-Navarrete et al. (2013), 43 patients with a follow-up time of 18 months, did not experience any changes in their AED regimen. The responder rate was 63% substantiating the efficacy of VNS.

The effect of VNS on seizure severity is still not unambiguously demonstrated, and since the severity of a seizure is not simple to measure objectively, there is no statistically powerful data of VNS reducing the seizure severity. Still, there is some proof and clinical experience of VNS not only reducing the number of seizures but also attenuating the seizures (Ravan, 2017, Krahl et al., 2003). The dominant hypothesis is that the VNS would reduce seizure severity. Ravan et al. (2017) evaluated the effects of closed-loop VNS on seizure severity by using quantitative features from a combination of EEG and ECG signals in 16 patients. Their results propose the on-demand stimulation reducing the spread of the seizure in EEG along with the reduced impact on cardiovascular function.

The selection of the VNS paradigm (rapid/medium/slow cycle) does not seem to have an unambiguous effect on the response. The median reduction in seizure frequencies in one study was 22% / 26% / 29%, respectively, the seizure reduction was 40% for all three groups combined. The responder rate also was the same for all three groups. (DeGiorgio et al., 2005).

VNS treatment does not seem to have effect in SMR or SUDEP rates (Granbichler et al., 2015). However, Ryvlin et al. (2018) published an extensive study with 40443 DRE patients with VNS, including 632 SUDEPs. During the follow-up after VNS implantation, the SUDEP rate decreased significantly suggesting a positive effect of VNS, although the finding possibly reflecting several factors, thus the real effect of VNS is still unexplained.

There is a hypothesis of a possible cardiac component in SUDEP. T-wave alternans (TWA) is an established marker for the risk of cardiac electrical instability and risk of SUDEP with patients with cardiovascular disease. In a study of 28 patients, Verrier et al. (2016) found out that VNS therapy was reducing TWA in 70% of the patients, therefore potentially reducing the risk. The effects took place only three weeks after implantation and lasting at least for a follow-up time of a year of the study. The reduced TWA by VNS was first found by Schamer et al. (2014).

Along with the effects on epileptic seizures, VNS might also have a beneficial effect on psychogenic nonepileptic seizures (PNES). In one study, 7 out of 11 patients experiencing epileptic seizures and PNES felt that the situation with their psychogenic seizures had improved. Although, the effect might be caused either from decreased epileptic seizure burden or the known effect on depression. (Vivas et al., 2017).

VNS can be considered a possible treatment option for refractory status epilepticus. Grioni et al. (2018) reported of children with super refractory status epilepticus, that were treated with VNS. In three out of four patients, the situation was significantly eased. A review article including 45 patients with refractory and super-refractory status epilepticus patients provided a result of VNS interrupting those conditions in 74% of the cases (Dibué-Adjei et al., 2019). In a case report of New-Onset Refractory Status Epilepticus (NORSE) patient, VNS reduced epileptiform activity significantly in EEG (Kurukumbi et al., 2019).

2.2.7.1.1 Efficacy of magnet mode stimulation

The VNS patients are equipped with a magnet bracelet to either stop the normal mode stimulation by placing the magnet on the pulse generator or to produce an additional stimulation by swiping the magnet over the pulse generator.

The first study assessing the efficacy of magnet mode stimulation included 35 patients of which only three were able to use the magnet by themselves. In two thirds of patients receiving magnet stimulations, the seizures were interrupted consistently or occasionally. (Boon et al., 2001). Morris (2003) analyzed the data of the E3 (VNS Study Group, 1995) and E4 (Labar et al., 1999) studies retrospectively to assess the efficacy of the magnet mode. In the data of the E3 study, treatment and control groups reported a cessation of 21.3% and 11.9% of seizures, correspondingly, and the difference was close to statistical significance, $p = 0.0799$. In the data of the nonrandomized E4 study, 86 (69%) out of 124 patients reported the usage of the magnet. 22% of them reported seizure termination, 31% seizure diminution, and

47% reported no effect. These results concluded, approximately half of the patients that used the magnet benefited from it. Patients with active magnets were more likely to report improvement in seizure situation than patients with inactive magnets. (Morris, 2003).

Fisher et al. (2015) published a critical review concerning the magnet mode, including altogether 859 patients. The on-demand magnet was reported beneficial in a weighted average of 45% of the patients (ranging from 0 to 89%) and the seizures were claimed to be cessated in a weighted average of 28% (ranging from 15 to 67%) of them. According to a register of Cyberonics (predecessor to LivaNova), containing 2696 patients, 61.8% of them used the magnet at least once. Within the users, 85.2% reported some benefit. With these patients, the magnet was applied by the patient only in 40% of instances.

2.2.7.1.2 Efficacy of automatic stimulation

In the study by Fisher et al. (2016), 20 patients experienced 89 seizures in the EMU (Epilepsy Monitoring Unit). The majority (28/38, 73.7%) of focal impaired awareness and focal to bilateral tonic-clonic seizures induced at least a 20% increase in heart rate. A substantial share (31/89, 34.8%) of seizures triggered the automatic stimulation and 19 out of 31 (61.3%) seizures cessated during the stimulation, with a median time of 35 seconds from seizure onset. Boon et al. (2015) included 16 patients with 66 seizures in their study. The majority (37/66, 56.1%) of the seizures induced at least 20% increase of heart rate, 27 out of 66 (40.9%) seizures were stimulated within ± 2 minutes of seizure onset and on 17 out of 66 (25.8%) seizures, triggered VNS overlapped with ongoing seizure activity. Of those 17 seizures, 10 (58.8%) stopped. These two studies summarized, patients had altogether 155 seizures and 58 (37.4%) of them led to the stimulation, and of those, 29 (50%) cessated the seizure. Of all seizures, 18,7% were detected and cessated by the automatic stimulation.

A recent, more extensive study presents altogether 113 patients with a follow-up time of three years. The material consisted of 51 fresh implantations and 62 patients with prior VNS. The newly implanted patients had a responder rate of 59%, while in the replacement VNS patients the additional responder rate was 71%. (Hamilton et al., 2018). The subsequent studies show similar results of the efficacy (Tzadok et al., 2019, Kawaji et al., 2020).

Boon et al. (2015) assessed also the number of automatic stimulations during physical (at least 3 minutes of stair-step) exercise. In 55.9% of 127 exercises, the

autostimulation was not triggered at all, in 20.5% of the sessions, it was triggered once and in 23.6% of them, twice.

2.2.7.2 Other effects in epilepsy patients

2.2.7.2.1 Overview

In addition to the seizure reduction in epilepsy patients, the patients usually report enhancement in mood, reduced daytime sleepiness, improved cognition, memory and quality of life (QoL). Children have been reported to show better verbal communication and performance in school. (Giordino et al., 2017, Ekmekci and Kaptan, 2019). VNS is proved to have positive effects on autonomic dysfunction and it is a cost-effective treatment choice. (Hirfanoglu et al., 2018, Ronkainen et al., 2006, Schomer et al., 2014, Verrier et al., 2016, Purser et al., 2018, Camp et al., 2015, Kopiuch et al., 2019)

2.2.7.2.2 Quality of life and cognitive functions

The effects of VNS were assessed in a meta-analysis (Panebianco et al., 2015). High and low-frequency (assumed subtherapeutic) stimulations did not cause statistically significant differences in QoL, cognition or mood.

The cognitive effects have been hypothesized to take place due to neural adaptation in the thalamocortical system. Shiramatsu et al. (2016) performed a research with eight rats. They investigated if VNS modulates stimulus-specific adaptation (SSA) in the auditory cortex and thalamus by using auditory evoked potentials with and without VNS. They found out that VNS weakened the SSA in the cortex but not in the thalamus, indicating that VNS have neuromodulatory effects on the cortical inhibitory system and in the thalamocortical projections, but not on the feedforward projections from the auditory periphery up to the thalamus. Among the VNS responders, there are results of VNS improving suppression of irrelevant information in decision making, therefore improving cognitive control (van Bochove et al., 2018).

In the studies included in the meta-analysis of Panebianco et al. (2015), slight improvement in the QoL was associated with responsiveness to VNS therapy. Some findings on QoL were found also with subtherapeutic VNS. In one uncontrolled

study, 96% out of 70 patients reported improvement in the QoL (Martorell-Llobregat et al., 2019).

As responsive VNS treatment reduces night-time epileptiform activities (IEDs and seizures), also awakenings reduce and therefore the sleep is more efficient (Ravan and Begnaud, 2019).

2.2.7.2.3 Effects on autonomic dysfunction

The effects of VNS on autonomic dysfunction has been assessed in several studies. Hirfanoglu et al. (2018) investigated the effects of VNS on cardiac functions with a hypothesis of VNS shifting the balance of the autonomic nervous system towards parasympathetic dominance. The cardiovascular system is known to be under a deep sympathetic influence in children with epilepsy. They found the beneficial effect of VNS taking place within first 6 months of therapy, but the it did not improve within the next 6 months. The HRV levels did not reach the levels of the healthy children. They propose that impaired cardiovascular autonomic regulation is associated with the epileptic process. As the impaired HRV within epilepsy patients is widely demonstrated with several studies, the effects of VNS on HRV are not unambiguous with contradictory results, which might be due to several parallel differing factors such as used AEDs, age, epilepsy duration, focus and seizure frequency (Ronkainen et al., 2006).

Along with the HRV, T-Wave Alternans (TWA) is another cardiac biomarker reflecting the function of the autonomic nervous system. The reduction of TWA by VNS was first reported by Schomer et al. (2014), and later confirmed for rVNS by Verrier et al. (2016), therefore proposing a cardioprotective role of VNS.

2.2.7.2.4 Socioeconomic aspects

Jennum et al. (2016) assessed whether VNS therapy has an effect on health costs, employment, and income level including 101 patients and 390 control patients, comparing the situations a year before implantation to 2 years after it. They discovered that VNS therapy was associated with fewer inpatient admissions and emergency room visits, and less frequent use of prescription medication. The employment status and income did not improve after the implantation, conversely, the number of patients on disability pension increased.

The economic effects of VNS therapy has been assessed in several studies with an unanimous conclusion that VNS is a cost-effective therapy (Purser et al., 2018, Camp et al., 2015, Kopiuch et al., 2019).

2.2.7.3 Predicting the responders to VNS

At present, there is no reliable way to predict the patients that will get a good response to VNS treatment. There are some studies concerning that issue. It is possible that some findings in EEG or HRV before VNS implantation could help in predicting the outcome. Also, some individual factors have been associated with a better response.

2.2.7.3.1 Individual factors predicting the response

Wang et al. (2019) published an extensive meta-analysis concerning the predictors of the outcome of VNS therapy. Altogether 1297 articles summarized, only a shorter duration of epilepsy before VNS implantation ($p = 0.038$) predicted good efficacy for VNS therapy. Age at VNS implantation, age at seizure onset, seizure types, etiology, and history of previous epilepsy surgery did not seem to have an effect on VNS response. They also hypothesize the role of several features in EEG and HRV, but the data are not sufficient to make any conclusions. In addition to those findings, there are, yet unpublished, data of intellectual disabilities reducing the efficacy of VNS therapy.

Although not concluded in the recent meta-analysis (Wang et al., 2019), there is some evidence and clinical experience on the different prognosis regarding to the seizure type. In a previous meta-analysis (Englot et al., 2011), evidence of greater reduction in seizure frequencies in generalized and mixed seizure types compared to focal seizures was presented. They also found statistically significant differences in relation to etiology, e.g. better response in patients with epilepsy due to a trauma or tuberous sclerosis in comparison to unknown etiology. In Lennox-Gestaut and Lennox-like syndromes the VNS seem to be effective especially on atypical absence and generalized tonic-clonic seizures but not on tonic seizures (Cukiert et al., 2013).

2.2.7.3.2 Predicting the response with EEG and brain imaging

Detecting the changes in the EEG synchronicity level could offer a potential predictive factor for the response to VNS. Patients responding to VNS seem to have a lower level of broadband EEG synchronization than non-responders (Bodin et al., 2015).

Bayasgalan et al. (2017) investigated the correlation between SCPs (slow cortical potentials) and the response to VNS. As a conclusion, they suggest that the positive polarity of scalp-recorded SCP shifts would be a possible predictor of good response to VNS treatment.

Moreover, an association between the P3 (P300) component of event-related potential and response for VNS therapy has been proposed. Wostyn et al. (2017) suggest an important role of the limbic system, insula and orbitofrontal cortex in the mechanism of action of VNS. They discovered a significant increase in P300 amplitude for responders and a significant decrease for nonresponders, the biomarker functioning better within nonmidline electrodes. De Taeye et al. (2014) support this finding by observing the activity of locus coeruleus with the P3 component. They discovered the VNS treatment inducing a significant increase of the P3 amplitude at the parietal midline electrode in EEG only in responders.

Kim et al. (2017) found that the patients with focal (either uni- or multifocal) epilepsy seem to respond to VNS therapy significantly better than the patients with generalized epilepsy ($p = 0.001$). In the study, they had 58 children with refractory epilepsy.

Since the effects of VNS are supposed to be mediated through the thalamus, there is a hypothesis that the intrinsic thalamic connectivity would be associated with the response to VNS therapy. Ibrahim et al. (2017) tested this hypothesis with 21 children by performing a resting-state fMRI (examination prior to the VNS implantation. They discovered that the better response to VNS therapy was associated with improved connectivity of the thalami to the anterior cingulate cortex (ACC) and to the left insula. Moreover, better performance in executive functions was associated with beneficial outcomes in ANT-DBS, possibly demonstrating better functional connectivity ANT-DBS and ACC (Järvenpää et al., 2018). Despite the similar response patterns (Kulju et al., 2018), it is unclear whether this finding could be extrapolated to VNS therapy.

Results of a recent study comprising 48 pediatric patients with VNS propose that median nerve somatosensory evoked field characteristics and functional connectivity could be used to predict seizure response to VNS (Mithani et al., 2020).

The pairwise derived brain symmetry index (pdBSI), that quantitatively measures symmetry in EEG, was tested with refractory epilepsy patients with VNS in relation to outcome. Controversially to the initial results in the validation study, pdBSI does not seem to be helpful for predicting responders to VNS. (de Vos et al., 2011, Hilderink et al., 2017).

2.2.7.3.3 Predicting the response with cardiac functions

Liu et al. (2017) measured heart-rate variability (HRV) interictally and before VNS implantation, to relate the findings to the outcome of VNS treatment. The findings of presurgical HRV measurements demonstrate that the patients that have higher parasympathetic cardiac control or vagal tone (equals higher HRV), were more likely to respond to VNS treatment. They also propose that patients suffering from focal seizures tend to have a better response to VNS therapy than patients with mixed seizures. In their subsequent studies, they emphasize these findings (Liu et al., 2018a) and propose that VNS increases the heart rate complexity (Liu et al., 2018b). Also, the findings of Yuan et al. (2017) suggest VNS shifting the balance of the autonomic nervous system towards parasympathetic dominance.

Chen at al. (2017) propose that response to VNS could be predicted by the heart rate during the seizure due to altered autonomous excitability. They hypothesize that the patients with ictal tachycardia are better responders than the patients with normal heart rate, and that it's inefficient in the patients with ictal bradycardia. This effect is proposed being associated with arterial baroreflex (ABR), which is an important mechanism maintaining the blood pressure, derived through the autonomic nervous system. When the blood pressure is high, ABR is hypersensitive and the autonomic neural response to the situation vagally excitatory. Conversely, when the blood pressure lowers, sympathetic excitability is increased and vagal excitability decreased, therefore causing the opposite effect to VNS and damping the effect of vagus nerve stimulation. As sympathetic excitability reduces and vagal excitability increases, the efficacy of VNS on epilepsy might improve.

2.2.8 Adverse effects, complications and contraindications

2.2.8.1 Complications

As summarized by Giordano et al. (2017) in their review, the complications of VNS can be divided in early (related to the surgery) and in late (related to the device and stimulation) complications as described below.

Early complications

- Intraoperative bradycardia and asystole during lead impedance testing (0.1%)
- Peritracheal hematoma
- Infections (3-8%)
- Vagus nerve injury causing hoarseness, dyspnea, and dysphagia. These complications are caused by left vocal cord paralysis, which is usually transient and patients normally recover after a few months.

Late complications

- Due to the device
    - Mostly late infections and wound dystrophy
    - Permanent left vocal cord paralysis due to the blunt trauma to the neck. Also, chronic stimulation could supposedly lead to denervation and paralysis
    - Tampering of the device in the obese and intellectually disabled patients ("twiddler's' syndrome")
    - Stretching of the nerve because of implantation of the lead electrode without enough strain loop relief
- Due to the stimulation
    - Delayed arrhythmias (bradycardia, asystole)
    - Laryngopharyngeal dysfunction
    - Obstructive sleep apnea
    - Stimulation of the phrenic nerve due to proximity
    - Tonsillar pain mimicking glossopharyngeal neuralgia
    - In children, increased drooling and hyperactivity have also been reported.

Laryngopharyngeal dysfunction (hoarseness, dyspnea, and coughing) is present approximately in 66% of patients and is usually not persistent. It is caused by the stimulation of the inferior (recurrent) laryngeal nerve and is directly related to the

stimulation frequency; the larger the frequency, the stronger the harm. Modification of surgical technique, i.e. lower neck incision, might have an effect on laryngeal complications (Vaiman et al., 2017).

2.2.8.2 Adverse effects

Panebianco et al. summarized in the Cochrane Collaboration article (2015) the most common adverse effects of VNS. They compared the patients receiving either high or low-level stimulation. Patients are considered as affected when they reported concerning adverse effects. Table 4.

Table 4. Adverse effects of VNS (Panebianco et al., 2015).

Adverse effect	n	n high stimu-lation	n low stimu-lation	n affected (high)	n affected (low)	total affected	RR (risk ratio)
Voice alteration and hoarseness	334	159	175	87 (54%)	44 (25%)	131 (39%)	2.17
Cough	334	159	175	51 (32%)	51 (29%)	102 (31%)	1.09
Dyspnea	312	149	163	27 (18%)	12 (7%)	39 (13%)	2.45
Pain	312	149	163	36 (24%)	39 (24%)	75 (24%)	1.01
Paresthesia	312	149	163	20 (13%)	28 (17%)	48 (15%)	0.78
Nausea	312	149	163	17 (11%)	21 (13%)	38 (12%)	0.89
Headache	220	105	115	24 (23%)	29 (25%)	53 (24%)	0.90

According to these results, voice alteration and hoarseness, and dyspnea are significant adverse effects of high stimulation. The occurrence of cough, pain, paresthesia, nausea and headache are similar in both groups. VNS is also proposed to cause ataxia, dizziness, fatigue, and somnolence, but none of the patients included in these studies reported of those adverse effects.

2.2.8.3 Discontinuation of VNS therapy & revision surgeries

2.2.8.3.1 Discontinuation of VNS therapy

The reasons for discontinuation of VNS may involve several reasons. The battery will deplete eventually over time - then the battery can be replaced in a small surgery without changing the electrodes around the vagus nerve, and at the same time, the pulse generator can be upgraded for a newer model. The side effects may be intolerable, there may be malfunctioning with the VNS device or a patient might request discontinuation for any reason. If the response to VNS therapy has not been desirable, it's possible to proceed with other neuromodulation therapies. Although, the response to VNS therapy may predict the response to ANT-DBS therapy, thus possibly predicting poor response also for ANT-DBS (Kulju et al., 2018).

2.2.8.3.2 Revision surgery

There are variety of reasons requiring a VNS revision surgery that could be device-related or due to other complications. Depending on the reason, the surgery could include the revision of the pulse generator or the electrodes, or both. The review of Giordano et al. (2017) presents a VNS device failure rate of 4 - 16.8%. Approximately a half of those failures led to revision surgery.

Couch et al. (2016) reported of 1144 VNS procedures in 644 patients. 46% of the patients required at least one revision surgery for the following reasons: battery depletion (27%), poor efficacy (9%), lead malfunction (8%), and infection (2%). Dlouhy et al. (2012) explained the reasons leading for 25 lead revision surgeries in 24 patients: intrinsic lead microlesions (64%), a visible fracture (12%), a short circuit (8%), and electrode coil dislocation (4%).

2.2.8.4 Contraindications

After a bilateral cervical vagotomy, the VNS treatment is naturally contraindicated. Patients with severe asthma or heart disease should be carefully evaluated before implantation of VNS due to the possibility of severe adverse effects. Also, patients that lay great importance to the quality of their voice, should be warned about the possible side effects. Children with swallowing difficulties might experience

worsening of the situation with VNS. For better management of those harms, patients may always turn the VNS device off with the magnet when needed. (Schachter and Schmidt, 2003).

VNS therapy might also worsen sleep apnea, which in some cases, could make a relative contraindication. The harm can usually be minimized with the change of settings and by using CPAP (Continuous Positive Airway Pressure) devices (Parhizgar et al., 2011). As sleep apnea is a relatively common disease in the population with efficient treatment options, the patients should be screened for possible sleep apnea before and after initiation of VNS therapy when suspected of sleep apnea (Salvadé et al., 2018). There is also a possibility of developing central sleep apnea when the solution could be an alteration in the VNS settings (Forde et al., 2017). There is also a case report of a patient that developed severe obstructive sleep apnea that was resolved only after the device was turned off (Gurung et al., 2020).

Usage of shortwave diathermy, microwave diathermy, and therapeutic ultrasound diathermy, are contraindicated with the patients having VNS. Diagnostic ultrasound is allowed. (Schachter and Schmidt, 2003). X-rays and CT-scans are allowed. MRI is allowed, as long as the device current is set OFF, but not at the region of the VNS device. Full-body MRI is contraindicated. (Cyberonics, 2014).

The safety of VNS therapy during pregnancy was evaluated in one study with a small group of patients only. They propose that VNS might increase the risk of obstetrical complications, but it is likely safe to the fetus. (Suller Marti et al., 2019).

2.2.9 Other modalities and indications

2.2.9.1 Transcutaneous VNS

Transcutaneous VNS (tVNS) modality is a relatively new alternative for implantable VNS system that offers a possibility for non-invasive neuromodulation therapy. The efficacy is proved, but the number of studies and the size of study populations are quite modest. (Ben-Menachem et al., 2015, Bauer et al., 2016, Barbella et al., 2018). Later a meta-analysis and a systematic review with three studies comprising 280 patients were published with a conclusion that tVNS is effective in seizure reduction. Although, only two of the studies included responder rates and the result was not statistically significant ($p = 0.45$). (Wu et al., 2020).

Due to the practical reasons, longer therapies with tVNS are not achievable, thus hypothetically the ideal efficacy of tVNS is not as desirable as with traditional VNS. The tVNS has been shown to activate the vagus nerve fibers similarly to the traditional VNS. (Simon and Blake, 2017).

Redgrave et al. (2018) performed a systematic review of the literature concerning the adverse effects of tVNS in human patients including altogether 1322 patients. The most common side effects were the following: local skin irritation (n = 240, 18.2%), headache (n = 47, 3.6%) and nasopharyngitis (n = 23, 1.7%). Only 35 patients (2.6%) dropped out of the studies due to the side effects and only three cases of serious adverse events were considered to be due to tVNS. Therefore, tVNS is considered a safe and well-tolerated treatment option, especially for the patients unwilling for surgical procedures.

Primary headaches (e.g. migraine and cluster headache) are proposed as alternative indications for tVNS with encouraging results (Simon and Blake, 2017).

2.2.9.2 Right-sided VNS (R-VNS)

The VNS is implanted on the left side to avoid cardiac side effects. The left vagus nerve mostly innervates the AV (atrioventricular) node of the heart and it is supposed to have less effect on the heart than stimulating the right vagus nerve, which mostly innervates the SA (sinoatrial) node of heart - stimulating the SA node could potentially cause bradycardia, asystole and other cardiac side effects (Giordano et al., 2017). However, there have been cases when implanting the VNS to the left side is impossible, e.g. because of the previous deep wound infection and VNS explantation. Therefore it was implanted to the right side, successfully and without severe complications (Spuck et al., 2008, Kahlow et al., 2013).

The outcome-related studies of R-VNS modality are limited to only several patient cases. The results show that R-VNS have antiepileptic efficacy and the side-effects are tolerable. The authors suggest of careful ECG follow-up during and after R-VNS implantation. (McGregor et al., 2005, Spuck et al., 2008, Navas et al., 2010).

2.2.9.3 VNS in depression

VNS therapy was approved for the treatment-resistant depression (TRD) in 2005 by the FDA. VNS is efficient in the treatment of TRD, the efficacy is assumed to be

involved with neurotransmitters (serotonin, norepinephrine) and signal transduction mechanisms. (Carreno et al., 2017, Roosevelt et al., 2006, Müller et al., 2017).

Comorbid depression is a common condition among patients with epilepsy, VNS showing efficacy to the depression symptoms as well (Conway et al., 2018). Spindler et al. (2019) investigated 59 patients with a follow-up time of a year. The severity of depression symptoms was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck's Depression Inventory (BDI). The decrease in depression scale scores was significant: MADRS 29 to 18 ($p < 0{,}001$) and BDI 24 to 14 ($p < 0{,}001$).

2.2.9.4 VNS in CNS injury

There is evidence of beneficial effects of VNS therapy in the recovery of brain injury. The effects are thought to be associated with excitated noradrenergic system, reduced post-injury seizures, hyperexcitability, anti-inflammatory effects, and attenuation of blood-brain barrier breakdown and cerebral edema (Neren et al., 2016).

The rat experiments offer some evidence of VNS improving the recovery from a brain injury (Roosevelt et al., 2006, Smith et al., 2005, Hays et al., 2016), although the results in humans are limited to some evidence of improved situation after an ischemic stroke (Ma et al., 2019).

2.2.9.5 VNS in inflammatory processes

The effects of VNS on inflammation, asthma, and pain are under investigation. VNS therapy has been found to have an influence on the production of inflammatory cytokines, thus attenuating the inflammatory response. Due to the systemic release of catecholamines, asthma attacks might be eased. VNS also induces antinociception by modulating multiple pain-associated structures in the brain and spinal cord, therefore potentially decreasing the sense of pain. (Yuan et al., 2016). In addition to that, VNS is also shown to have efficacy in the treatment of sepsis, lung injury, rheumatoid arthritis, and diabetes (Johnson et al., 2018). Due to the relationship between chronic inflammation and autonomic functions, VNS reducing autonomic dysfunction might have a positive effect on chronic inflammatory processes (Leal et al., 2018).

The vagus nerve is a major mediator of gut-brain communication and is highly involved in monitoring systemic inflammation. When detecting inflammatory cytokines, the nerve's afferent connections transmit the information to the hypothalamus, which in turn activates the vago-vagal cholinergic anti-inflammatory pathway, vago-sympathetic anti-inflammatory pathway, and the hypothalamic-pituitary-adrenal (HPA) axis. The vago-vagal pathway corresponds to the vagus nerve's efferent connections, which are largely cholinergic and are believed to modulate an anti-inflammatory pathway through nicotinic acetylcholine receptors, which in turn activate several cellular anti-inflammatory mechanisms in addition to modulating autonomic control of other organs such as the heart, lungs, and gastrointestinal tract. VNS is suggested to evoke HPA axis increasing the secretion of cortisol. (Borovikova et al., 2000, Wang et al., 2003, Lu et al., 2014, Olofsson et al., 2012, Hachem et al., 2018)

Furthermore, the vago-sympathetic anti-inflammatory pathway may mediate a significant reduction in inflammatory cytokines in multiple organs mediated via the greater splanchnic nerve. (Martelli et al., 2014, Komegae et al., 2018, Bratton et al., 2012). Also, the HPA axis represents a slower, hormonal response to long-term or circadian patterns of inflammation, which can be monitored by assessing serum cortisol levels (Weitzman et al., 1971). Some epileptic seizure types present a similar circadian variation to serum cortisol concentration (van Campen et al., 2015).

2.2.9.6 Other indications

VNS therapy has the FDA's approval for the treatment of obesity. The effect on decreased food consumption and therefore decreasing weight gain was first proved in animal experiments (Val-Laillet et al., 2010). However, the weight-loss efficacy has conflicting results from not significantly having an effect on weight (Bodenlos et al., 2014) to being efficient in losing weight (Burneo et al., 2002). The effect is probably mediated through diminished food craving (Bodenlos et al., 2007). A rat experiment suggests that the effects are mediated by delaying gastric emptying by enhancement of vagal activity and the release of anorexigenic hormones (Dai et al., 2020).

Rat exams demonstrate the effects of VNS on glucose metabolism; afferent VNS increased blood glucose levels and inhibited insulin secretion in rats, proposing the increased risk of developing impaired glucose tolerance or even diabetes mellitus (DM) in VNS patients. On the other hand, selective efferent VNS might be a treatment option for DM as it induces the secretion of insulin. (Stauss et al., 2018, Meyers et al., 2016). Although, the pathogenesis of DM is not that unambiguous,

including also inflammatory processes. The net effect of VNS is proposed to reduce the risk of developing DM (Johnson et al., 2018).

Vagus nerve stimulation seems to improve working memory performance and emotional reactivity immediately in humans (Sun et al., 2017). VNS therapy also resulted in longer reaction time and greater frontal alpha asymmetry in response to threat-related distractors in that study. Clark et al. (1999) examined word-recognition memory in and propose VNS enhancing verbal learning significantly.

A pilot study (Tyler et al., 2017) proposes the efficacy of VNS in tinnitus, some subsequent findings enhancing this finding (Wichova et al., 2018).

There is a case report of a patient, who was in a vegetative state for over 15 years after a car accident. He was implanted with a VNS. Already after three months, increased brain activity was found along with clinical effects showing reproducible and consistent improvements in general arousal, sustained attention, body motility, and visual pursuit. (Corazzol et al., 2017).

2.3 DBS therapy for epilepsy

2.3.1 Overview and principle of action

Along with the electrical stimulation of the vagus nerve, neuromodulation therapy options for refractory epilepsy also include deep brain stimulation (DBS) and cortical stimulation. In DBS therapy, there are multiple sectors in the brain that can be stimulated to disrupt epileptic seizures. The most common sectors are the anterior nucleus of the thalamus (ANT), centromedial nucleus of thalamus, cerebellum, hippocampus and nucleus accubens. Closed-loop ictal onset zone stimulation and cortical stimulations are also possible. (Sprengers et al., 2017). This chapter concentrates on ANT-DBS therapy, which is the most widely studied target in DBS. ANT plays a crucial role in the spreading of a seizure, therefore stimulation of ANT affecting the seizure propagation. (Zangiabadi et al., 2019).

The precise mechanism of action in DBS therapy is still not fully understood, but there are some hypotheses. The continuous electrical current might inhibit the targeted brain structures functionally. This effect is reversible since the stimulation can be stopped at any time. The inhibiting effect depends on the location of electrodes; if implanted to the epileptic zone, it might lead to local inhibition at the seizure onset zone, whereas when implanted to the structures important in seizure

propagation, stimulation might prevent seizures from spreading - e.g. the ANT. (Sprengers et al., 2014).

2.3.2 Surgery

The DBS system consists of the pulse generator implanted in the upper chest, macroelectrodes implanted in the brain, and the leads connecting the pulse generator to the electrodes. Surgical strategies vary with the surgical teams; in this chapter, the surgical technique is referred from the article of Machado et al. (2006) and the local details of procedure in Tampere University Hospital have been gathered from the article of Lehtimäki et al. (2016).

The stereotactic surgeries are pre-planned with a computer program. By using recent MRI images the targets for the electrodes are localized and the trajectory is planned.

After the precise planning of the operation, the patient is anesthetized and a head frame is placed. The preoperative computed tomography (CT) scan is taken and the MRI and CT scans are merged to obtain the precise coordinates regarding the head frame.

The scalp is prepared for the surgery. The entry points are marked on the skin with the help of the stereotactic arc, and the incisions are planned. The holes are drilled in the skull from the same angle than the electrodes will be applied. Target definition accuracy can be supplemented with microelectrode recording (MER), though its feasibility in ANT-DBS surgery is unclear (Järvenpää et al., submitted). The DBS leads (macroelectrodes) are implanted to the target and the localization of the electrodes may be verified with perioperative X-rays. The lead is anchored and secured. After securing, the lead is attached to the extension wire that is tunneled under the scalp and strain relief is made with the excess lead. The pulse generator is implanted into the upper chest similarly to VNS implantation, and the lead is connected to the pulse generator.

In Tampere University Hospital, the stimulator is typically turned on at the fifth postoperative day using 1 min ON and 5 min OFF cycle, 140 Hz, 90 μs pulse width. The stimulation amplitude is elevated to 5 V within a couple of weeks.

2.3.3 ANT-DBS

2.3.3.1 Prognosis

Fisher et al. (2010) evaluated in the SANTE (stimulation of the anterior nucleus of the thalamus) trial the effects of bilateral electrical stimulation of the ANT in patients with refractory focal epilepsy. The study population (n = 110) was multicentered, double-blinded and randomized. In the trial, the first 3 months was a blinded phase when half of the patients received stimulation and half of them did not. After that, all the patients received stimulation.

In the last month of the blinded phase the patients that received stimulation had a 29% greater reduction in seizure frequencies. The absolute mean seizure reduction in the blinded phase was 14,5% in the control group and 40.4% in the stimulated group. Epilepsy-related injuries were significantly reduced in the stimulation group (7.4% versus 25.5%). During the blinded phase, there were no significant differences in responder rates or patients with seizure freedom. By 2 years of follow-up, 54% of the patients had at least a 50% reduction in seizure frequency. 13% of the patients were seizure-free for at least 6 months during the 2 year follow-up period. A subsequent study provided 5-year follow-up data of the same patients (Salanova et al., 2015). At 5 years, mean seizure reduction was 69%, and 16% of the patients were seizure-free for at least 6 months.

Changes in neuropsychological test scores for cognition and mood were not statistically different in the stimulation and the control groups. Changes in the quality of life were neither statistically nor clinically significant. (Fisher et al., 2010). Although, in the follow-up study, quality of life was significantly improved (Salanova et al., 2015).

Lehtimäki et al. (2016) assessed the optimal stimulation target in the ANT. They followed prospectively 15 patients with refractory epilepsy for more than 5 years. They had 62 contacts in 30 treatment attempts, forming a conclusion of the antiepileptic effect probably being dependent on localization of electrodes in ANT-DBS treatment, especially in anterior-posterior axis. The treatment was more effective when stimulating the ANT more anteriorly: 17 out of 23 (74 %) contacts that led for a good response were anterior and 30 out of 36 (83 %) contacts that were posterior, did not lead for a good response. They also concluded that due to extensive anatomical variation, direct visualization of the target is essential instead of approximation according to an anatomical atlas.

2.3.3.2 Adverse effects and complications

This chapter is summarized from the results of the SANTE trial and its follow-up trial including 110 patients (Fisher et al., 2010, Salanova et al., 2015).

None of the participants had symptomatic hemorrhage (although there were 5 asymptomatic hemorrhages within the first year) or brain infection. Ten of the patients (9.1%) had implant site infections within the first month after the operation and within five years, 12.7% of the patients did. In five patients (4.5%) the initial infection led to explantation whereas within five years the explantation rate was 8.2%.

In 8.2% of the patients, the electrodes were not implanted into the target structure, requiring a replacement procedure. Implant site pain was reported by 10.9% of the patients within the first year and by 20.9% after five years.

Five patients (4.5%) experienced status epilepticus during the first year after the implantation. One of them was during the blinded phase of the study, receiving stimulation. One of the patients experienced status epilepticus after turning the device on after the blinded phase, SE resolving within 5 days after turning the device off. Along with that, one patient experienced 210 focal impaired awareness seizures in three days after turning the stimulation on, as the baseline was 19 seizures per month. The situation resolved after reprogramming the stimulator.

Depression and subjective memory impairment were self-reported significantly more frequently within the stimulation group; 14.8% versus 1.8% and 13.0% versus 1.8%, respectively, during the blinded phase of the study.

Other adverse effects reported by the patients were not statistically significant when compared to the control group; the patients reported of confusional state (7.4% versus 0.0%), anxiety (9.3% versus 1.8%), paraesthesia (9.3% versus 3.6%), new or worse focal to bilateral tonic-clonic (9.3% versus 5.5%), focal aware (5.6% versus 1.8%) or impaired awareness (9.3% versus 7.3%) seizures. (Sprengers et al., 2014).

2.3.3.3 Other indications for DBS treatment

Along with the treatment of epilepsy, deep brain stimulation can be used in the treatment of an increasing number of other pathologies by stimulating different nuclei in the brain.

In addition to Parkinson's disease and other movement disorders, DBS might have beneficial effects in repairing neural tissues and for neurodegenerative

pathologies along with psychiatric and behavioral dysfunctions, such as schizophrenia, bipolar disorder, obesity, anorexia, drug addiction, and alcoholism. DBS may be also functional in the treatment of a number of cognitive dysfunctions. (Nicolaidis, 2017).

3 AIMS OF THE STUDY

1. To assess if there are similarities between the clinical responses to VNS and DBS treatments.

2. To assess how the initiation of responsive VNS therapy affects the outcome and power usage.

3. To assess the additive effect of autostimulation mode and different stimulation settings on the function of VNS, and the autostimulation performance in different epilepsy types.

4. To assess the circadian rhythmicity of automatic stimulations in rVNS therapy in different epilepsy types.

4 MATERIALS AND METHODS

4.1 Patients

In all four studies altogether 42 patients were included. All the patients suffer from refractory epilepsy and receive VNS therapy. The patients were treated in the Outpatient Clinic of Neurology and Rehabilitation, Tampere University Hospital. Due to some patients living in other cities, the follow-up was partly actualized in Seinäjoki, Vaasa or Hämeenlinna central hospitals, by the same neurologist. Seizures were classified according to the new ILAE classification for seizures (Fisher et al., 2017).

Altogether 42 patients are included, the study populations of study II, III and IV overlap. The study population of study I is separate. Figure 5.

All the surgical procedures were performed in Tampere University Hospital. The VNS implantations took place in 2005-2017 and DBS implantations in 2010-2013. Before the implantations, all patients were evaluated using inpatient video-EEG (electroencephalography) telemetry, 18-F-FDG-PET (Fluorodeoxyglucose-positron emission tomography) and 3T MRI (3 Tesla Magnetic Resonance Imaging) to identify potential epileptogenic zone/epileptic syndrome and evaluated for resective surgery.

Figure 5. Illustration of follow-up times of the patients in all four papers. The patients in the first paper are the cohort I and patients in the second paper are the cohort II. In the third and the fourth paper, the patients are the same, cohort III. In cohort I the baseline is the previous 12 months before the VNS therapy. In three patients before initiation of ANT-DBS therapy the VNS device was off, forming a separate OFF-time. In cohort II the baseline is the time of patients receiving traditional VNS therapy for the last 12 months before the implantation of the VNS model 106. Before implantation of VNS model 106, the device was OFF, forming a separate OFF-time in three patients. In cohort III the patients of the cohort II are included except for one patient due to lacking autostimulation data. In addition to that, 17 patients with VNS model 106 without prior VNS therapy were included. The fourth illustration elucidates the overlapping of the cohorts.

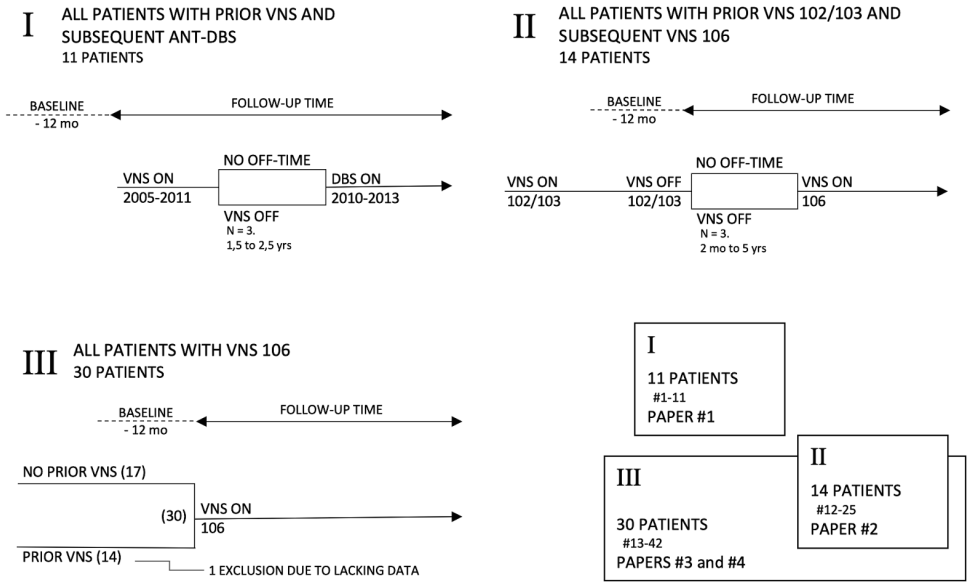


Table 5. Patient characteristics.

	Study I	Study II	Studies III and IV
Study population	11	14	30
Patients	#1 - #11	#12 - #25	#13 - #42
Study	#1	#2	#3 and #4
Gender			
Males	8 (73 %)	5 (35.7 %)	11 (36.6 %)
Females	3 (27 %)	9 (64.3 %)	19 (63.3 %)
Age at VNS implant			
Range	from 17 to 49	from 16 to 62	from 16 to 62
Mean	27,9	36.3	34,2
SD	11,3	11.7	9.8
MRI findings			
Normal	5 (45,5 %)	5 (35.7 %)	9 (30.0 %)
Abnormal	6 (54,5 %)	9 (64.3 %)	21 (70.0 %)
Etiology			
CD	5 (45 %)	5 (35.7 %)	7 (23.3 %)
Encephalitis	4 (36 %)	1 (7.1 %)	2 (6.7 %)
Postradiation	0	1 (7.1 %)	1 (3.3 %)
Labrune's disease	0	1 (7.1 %)	1 (3.3 %)
Perinatal vascular lesion	0	1 (7.1 %)	1 (3.3 %)
Tuberous sclerosis	0	0	3 (10.0 %)
Brain tumor	0	0	2 (6.7 %)
ADNFLE	0	0	1 (3.3 %)
Dravet syndrome	0	0	1 (3.3 %)
Sturge-Weber sdr	0	0	1 (3.3 %)
Developmental	0	0	2 (6.7 %)
Unknown	2 (18 %)	5 (35.7 %)	8 (26.7 %)
Seizure onset zone			
TLE	3 (27,3 %)	6 (54,5 %)	9 (30.0 %)
ETLE	1 (9,1 %)	4 (28,6 %)	9 (30.0 %)
MFE	7 (63,6 %)	4 (28,6 %)	11 (36.7 %)
Unknown	0	0	1 (3.3 %)
Seizure types			
FAS		5 (35.7 %)	11 (36.7 %)
FIAS		12 (85.7 %)	26 (86.7 %)
FBTCS		2 (14.3 %)	10 (33.3 %)
PNES		1 (7.1 %)	0
GTCS		0	1 (3.3 %)
Other neuromodulation			
Prior VNS	0	14 (100 %)	13 (43,3 %)
Subsequent DBS	11 (100%)	0	0
Prior epilepsy surgery			
yes			3 (10.0 %)
no			27 (90.0 %)

4.1.1 Study I

In study I we included all the patients that received subsequent ANT-DBS therapy after traditional VNS therapy, a total of 11 patients. All of them received traditional VNS therapy with cyclic normal mode and on-demand magnet mode stimulations. The patients received traditional VNS therapy as long as it lasted efficiently, whereas the decision of subsequent treatment with ANT-DBS was made. The VNS therapy was discontinued due to battery depletion, lacking efficacy or a high impedance situation, and the VNS system was explanted in 10 out of 11 patients; in one patient the VNS was turned off, but not explanted. All the patients were subsequently implanted with the ANT-DBS system.

We evaluated the number of seizures for the baseline of a year before the initiation of VNS therapy, during the whole VNS therapy, and during DBS therapy.

4.1.2 Study II

In study II we included all the patients subsequently implanted with VNS model 106 AspireSR® and received VNS therapy with rVNS, after traditional VNS therapy with VNS. In this study, we had 14 patients. 12 of the patients had prior 102, and 2 patients had prior 103 models of VNS. The reason for revision surgeries was upcoming battery depletion.

Five of the patients were followed up in other Finnish hospitals prior to the referral for the reimplantation in our center. The battery was depleted in four of them, therefore forming a separate OFF-period before initiating the new VNS model. After the reimplantation, the responsibility of the treatment stood at Tampere University Hospital.

4.1.3 Studies III and IV

In studies III and IV we included all the patients implanted with VNS model 106 AspireSR® and received VNS therapy with rVNS, with an exception of one patient, that had lacking follow-up data of automatic stimulations and was excluded. In these studies, a total of 30 patients were included. 13 of the patients (43.3%) received prior VNS therapy, and mostly (n = 10, 76.9%) the pulse generator was changed due to battery depletion. Other reasons for device replacement were a high impedance situation in two (15.4%) patients requiring revision surgeries. Another one of those

two patients also had a wound infection requiring another revision surgery. One (7.7%) of the patients was first considered as a nonresponder and the VNS device was off for five years, but the patient was re-evaluated for the VNS treatment. This patient is considered as fresh implantation due to lacking pre-106 information and a long non-stimulated period of time.

In all the outpatient clinic visits, autostimulation timestamp data and programmer settings were saved along with seizure diary data. In the third study we analyzed the data in stimulation periods and in the fourth study we analyzed the autostimulation timestamp data.

4.2 Methods

4.2.1 Study I

In order to compare the long term response to consequent VNS and DBS therapies, we built individual seizure frequency curves for every patient for the follow-up time, (means of consequent six month periods). The long term response was grouped in three; progressive response, partial response, and no response. The "partial response" patients had initially at least a 50% decrease in seizure frequency with fluctuating seizure count over the long-term. Since the effect does not sustain, they cannot be considered as real responders.

The responses for the two consecutive neuromodulation therapies were evaluated. The total follow-up time of the patients varied from 7 to 11 years.
In order to evaluate the possible confounding factors, we also assessed the alterations in the patients' drug regimen during the follow-up.

4.2.2 Study II

In study II we compared the efficacy, the number of daily stimulations and the total amount of electrical charge used between traditional VNS therapy and the responsive VNS therapy with autostimulation mode.

We counted the number of daily stimulations as a percentage of ON-time, also known as therapy time (separately normal mode, AutoStim mode and magnet mode). We also counted the total amount of electrical charge (in Coulombs) delivered in 24 hours. Also, we have accurate data of VNS settings and the total number of VNS

activations, separately automatic, normal mode and magnet mode activations, as a daily average.

We had reliable seizure diary data for 11 out of 14 patients to assess the seizure control in regard to stimulation parameters. The baseline in the seizure frequencies was the average number of the seizure counts for 12 months with the older model of VNS. With the model 106, the seizure counts were monthly averages during consecutive periods of 6 months. The follow-up varied from 7 to 32 months (mean 18.1 and SD 8.1).

A patient was considered as a responder, if for the most part of the follow-up with model 106, the seizure reduction was at least 50% or the progressive improvement in seizure frequency led to at least 50% decrease, when assessing the disabling seizures, e.g. seizures interrupting activities of daily living in comparison to the pre model 106 era. Along with the total number of seizures, we also analyzed the severity of seizures. The seizure severity analysis was based on the subjective experience and reported duration of the seizures.

For assessing the alteration in the charge delivered to the patients, we calculated the total charge with the latest (assumed as the most efficient) stimulation settings with older VNS model, and with the latest new VNS model settings.

4.2.2.1 Counting the total charge in VNS therapy

The amount of electrical charge delivered to the patients is dependent on the stimulation settings and the number of stimulations.

In the second and third papers, the theoretical total charge (Q, Coulombs) was calculated to assess quantitative data of the total amount of electrical stimulation delivered in the patients. Therefore, the "VNS dose" could be assessed in all the patients independently of the number of stimulations and used stimulation settings to return comparable numerical values for the delivered stimulation.

For patients receiving normal mode cyclic stimulation only, we used the following formula (Aaronson et al., 2013).

$$Q_{total} = \left(\frac{T_{period}\left(\frac{I}{1000}\right)\left(\frac{Pw}{10^6}\right)f(t_{ON}+4)}{t_{ON}+(t_{OFF}*60)}\right)$$

Q_{total} = total charge (C), T_{period} = time period (sec), I = output current (mA), Pw = pulse width (msec), f = pulse frequency (Hz), t_{ON} = ON-time (sec), t_{OFF} = OFF-time (min).

T_{period} is 86400 seconds in this analysis, equals one day.

To return the total Q for the patients receiving VNS therapy with rVNS, we calculated the t_{OFF} value as follows (Heck et al., 2002). The ON% value, therapy time, is the percentual time of active VNS stimulation, data fetched from the VNS device. The additional four seconds were added to the ON-time to account for ramping periods during the initiation and termination of stimulation bursts (Aaronson et al., 2013).

$$t_{OFF} = \frac{t_{ON} + 4}{ON\%} - t_{ON}$$

t_{OFF} = OFF-time (sec), t_{ON} = ON-time (sec), ON% = therapy time (%/100).

4.2.3 Study III

In study III we described the additive effect of autostimulation mode and different stimulation settings on the function of VNS, and compared the autostimulation performance in different epilepsy types.

The follow-up time started when AutoStim mode was initiated, averagely 53 days after implantation, and the data was collected until a selected endpoint, October 2017.

We conceptualized the device setting data as a "stimulation period", e.g. unaltered stimulation settings and the average number of delivered stimulations between two outpatient clinic visits. The stimulation period (SP) contains parameters for Output Current (mA), pulse width (μsec), frequency (Hz), signal ON-time (sec), signal OFF-time (min) and the threshold for AutoStim (%). Therapy information included the number of stimulations delivered in different categories (normal and autostimulation mode) as the daily average in a given stimulation period and therapy time as a percentage of total ON-time. Magnet mode data were excluded from the analysis due to a negligible amount of stimulations. The total dataset for 30 patients consisted of 208 stimulation periods.

To assess the total electrical charge, we used the same formulas as in the second paper.

First, we divided the patients into four groups according to the seizure onset zone; TLE, ETLE, MFE and ALL (temporal lobe, extratemporal lobe, and multifocal epilepsies, and all patients) to assess whether the seizure onset zone has an effect on the number of the stimulations. We analyzed the effect of autostimulation threshold rate on the autostimulation count within all epilepsy types separately.

In the second analysis, we extracted a dataset (25 SPs), where the following parameters were the same; Output Current 1.75mA, frequency 30Hz, pulse width 250usec, ON-time 30 sec, and the autostimulation threshold 20%. In this dataset, we analyzed how altered OFF-time affect the number of normal mode and responsive stimulations and total charge. We also counted the total charge without autostimulation to assess the additive effect of responsive VNS.

In the third analysis, the dataset with 5-minutes OFF-time was performed to compare the number of autostimulations with the thresholds of 40% and 20%.

4.2.4 Study IV

In study IV, the number and clustering of automatic stimulations in different times of day were evaluated and the pattern of clustering was compared between different types of epilepsy. In this study we developed a new concept of automatic stimulation clustering.

We downloaded the data of all the delivered automatic stimulations as timestamps. The capacity of saved entries in VNS device is limited; maximum number of entries downloaded at once was 3500 units. The total number of stimulation periods was 167. Mean follow-up time was 13.1 months per patient, ranging from 5.4 to 18.9 months. The cumulative follow-up time was 11822 days, i.e. more than 32 years. Follow-up time has been counted as a time period between the first and the last saved autostimulation. Due to the limited amount of saved autostimulations, there are gaps in the follow-up.

Autostimulation data containing thresholds and timestamps were analyzed in Matlab (MathWorks, Natick, MA) using a custom software. All the timestamps are single autostimulation events where a heart rate change was detected and additional therapy was applied.

The raw-data of the automatic stimulations was built for a 24-hour histogram, automatic stimulations binned by an hour. In this method, circadian trends were apparent but qualitatively weak. In the further analysis, we developed a concept of automatic stimulation clustering to rule out potential non-seizure related single automatic stimulations; several automatic stimulations occurring in a short period of time might represent real seizure-related activations with a better probability. A clustered autostimulation was defined as any autostimulation that occurred within the duration of the therapeutic cycle during the therapy OFF-time, compared to both the previous autostimulation and the following autostimulation. Non-clustered

autostimulations were removed from the dataset and 24-hour histograms were prepared again.

In cases where statistical analysis was performed in this dataset, 95% confidence intervals were calculated and compared between groups. The data included in these analyses contained autostimulation data derived from patients set to any threshold level for autostimulation detection, as the clustering method efficiently excluded errant autostimulations and made the data from different threshold levels appear similar.

4.2.5 Seizure counts

The seizure frequency data is mainly based on the original seizure diaries gathered from the patients. Depending on the independence level of patients, the seizure diaries are maintained by the patients themselves, or by the family or the caregivers, if the patients are intellectually or physically disabled.

When assessing the response, we mainly utilized traditional division for responders and nonresponders; a patient is considered as a responder if seizure count decreased at least for 50%, otherwise a nonresponder.

All the patients have their own habit of noting the seizures to the diaries. Most of the diaries are on paper; in a single sheet of paper, there is a slot for every day in every month for a year. Patients note down every seizure to an adequate slot. Before starting to use the diaries, the different seizure types are classified and a specific mark for each seizure type is defined with a registered nurse or an epileptologist. Therefore we have seizure follow-up data with an accuracy of a day, with a classification of seizures. Some patients use digital seizure diary systems with a mobile application. Some patients have their own system of keeping track of seizures, for example in a calendar. For shorter periods of time the seizure frequencies can be assessed from the video-EEG studies, for up to four days, or video-based night-time registration systems of seizures at home or ward, for up to a month.

Since the most of the seizure frequency data is based on the manual diaries, it was not accurate. Some of the patients may be reluctant to note down all the seizures, some of them are not able to do it at all. Sometimes they don't notice the seizures themselves at all because of the impaired awareness or because of being asleep. Also, some of the patients experience PNES (psychogenic non-epileptic seizures) and are not able to differentiate them from epileptic seizures.

Some of the patients started the punctual follow-up of seizure counts only after the initiation of VNS treatment. To assess the baseline seizure frequency data from the time before the operation, we used the patient files of the outpatient clinic visits. Usually, the current situation of the disease is described in the reports, including the current frequency of the seizures, but in some cases not very accurately.

4.2.6 The devices

4.2.6.1 VNS - the device

The patients included in these studies have three different models of VNS device implanted: the models 102 (VNS Pulse), 103 (VNS Demipulse) and 106 (VNS AspireSR). The devices are manufactured by LivaNova (former Cyberonics). Whereas older models have two-pin connections to the lead electrodes, newer ones have a single pin. Newer models may also be smaller with an ability to detect the heart rate.

The implanted VNS system consists of the pulse generator, coil electrode, and wires. The coil electrode includes three helical contacts; two are active contacts, third is an anchor. The battery is estimated to last from 6 to 8 years. The device is programmed with an external device connected to the pulse generator with a programming wand. The wand is placed on the pulse generator and the programming and fetching of information are performed with a touch-screen tablet device.

The adjustable settings of different VNS models are presented in Table 6. The physical appearance of the devices 102 and 106 are the same - the model 103 is slightly smaller, therefore requiring shorter skin incision causing less cosmetic harm and discomfort in the patients. Model 102 has been available since 2002, model 103 since 2007 and model 106 since 2014.

Table 6. Adjustable parameters of VNS pulse generator (Cyberonics Physician's Manual, July 2015). All of the parameters are adjustable independently in the normal, magnet, and autostimulation mode settings. The heartbeat sensitivity setting is the sensitivity for detecting the R-waves in ECG. The most sensitive value is 5, and the least sensitive value is 1. In the threshold for AutoStim, the lowest setting is the most sensitive.

Tab	Parameter name	Generator model(s)	Programmable values
Normal	Output Current (mA)	101, 102(R), 103, 104, 105	0.00-3.50 mA, in 0.25 mA increments
		106	0.000-2.000 mA, in 0.125 mA increments; 2.000-3.500 mA, in 0.250 mA increments
	Signal Frequency (Hz)	101, 102(R), 103, 104, 105, 106	1, 2, 5, 10, 15, 20, 25, 30 Hz
	Pulse Width (µSec)		130, 250, 500, 750, 1000 µSec
	Signal ON Time (Sec)		7, 14, 21, 30, 60 Sec
	Signal OFF Time (Min)		0.2, 0.3, 0.5, 0.8, 1.1, 1.8, and 3 min; 5 to 60 in 5-min steps; 60 to 180 in 30-min steps
Magnet	Output Current (mA)	101, 102(R), 103, 104, 105	0.00-3.50 mA, in 0.25 mA increments
		106	0.000-2.000 mA, in 0.125 mA increments; 2.000-3.500 mA, in 0.250 mA increments
	Pulse Width (µSec)	101, 102(R), 103, 104, 105, 106	130, 250, 500, 750, 1000 µSec
	Signal ON Time (Sec)		7, 14, 21, 30, 60 Sec
AutoStim	Output Current (mA)	106	0.000-2.000 mA, in 0.125 mA increments; 2.000-3.500 mA, in 0.250 mA increments
	Pulse Width (µSec)		130, 250, 500, 750, 1000 µSec
	Signal ON Time (Sec)		30, 60 Sec
Tachycardia Detection	Tachycardia Detection	106	ON, OFF
	Heartbeat Detection (sensitivity)		1, 2, 3, 4, 5
	Threshold for AutoStim (heart rate change) (%)		20, 30, 40, 50, 60, 70 %

4.2.6.2 DBS - the device

In the first study, 11 patients with DBS system were included. The devices (leads 3389 and the pulse generator Activa PC) are manufactured by Medtronic. The DBS leads were stereotactically implanted bilaterally into the ANT. An internal pulse generator was implanted into the subcutaneous upper chest. DBS was started within a few days after surgery.

The Activa PC is a dual-channel neurostimulator device that delivers bilateral stimulation with a single device. It contains a non-rechargeable battery and microelectronic circuitry to deliver a controlled electrical pulse via the leads to the targeted areas in the brain. The programmable parameters of the device are presented in Table 7. The device is programmed similarly to the VNS device, with an external programming device with a wand to be placed on the pulse generator.

Table 7. Adjustable parameters of DBS Activa PC neurostimulator (Medtronic Activa PC Implant Manual, 2008)

Programmable parameter	Operating range and resolution [a]
Number of defined groups	1 to 4
Number of programs per group	1 to 4
Electrode configuration [b]	1 to 4 electrodes per lead as anode (+), cathode (–), or Off; case defined as anode or Off
Amplitude (voltage mode)	0 to 10.5 V with 0.05-V or 0.1-V resolution
Amplitude (current mode)	0 to 25.5 mA with 0.1-mA resolution
Amplitude – upper patient limit	Tracking limit (by hemisphere): +0 to +2 (0.2 resolution); +2 to +4.5 (0.5 resolution)
Amplitude – lower patient limit	Tracking limit (by hemisphere): -0 to -2 (0.2 resolution); -2 to -4.0 (0.5 resolution); full range [c]
Pulse width	60 to 450 µs (10-µs resolution)
Pulse width - upper patient limit	Tracking limit: +0 to +100 µs (10-µs resolution)
Pulse width - lower patient limit	Tracking limit: -0 to -100 µs (10-µs resolution)
Rate (voltage mode)	2 to 250 Hz (resolution: 1 Hz from 2 Hz to 10 Hz, 5 Hz from 10 Hz to 250 Hz)[d]

Rate (current mode)	30 to 250 Hz (5-Hz resolution)[d]
Rate – upper patient limit	Tracking limit: +0 to +50 Hz (10-Hz resolution)
Rate – lower patient limit	Tracking limit: -0 to -50 Hz (10-Hz resolution)
SoftStart/Stop	Off, On: 1-, 2-, 4-, or 8-second ramp duration
Cycling	Off, On: 0.1 s to 24 hr (resolution: 0.1 s from 0.1 s to 1 s, 1 s from 1 s to 59 s, 1 min from 1 min to 59 min, 1 hr from 1 hr to 24 hr)

[a] Interlocks will prevent the use of some parameter combinations.
[b] In current mode, a maximum of 2 electrodes (including the case) can be configured as anode (+) and cathode (–).
[c] Full range = -10.5 V (voltage mode); -25.5 mA (current mode).
[d] Rate limited to 125 Hz when two programs are active on a single lead

4.2.7 The protocol for VNS at Tampere University Hospital

4.2.7.1 Procedures before the implantation

The inclusion criteria for VNS therapy in Tampere are the following:

a) refractory epilepsy with seizures decreasing the quality of life considerably,
b) epilepsy surgery not possible or seizures persist after the surgery,
c) VNS therapy is neuropsychologically, and
d) psychically applicable.

All the patients are evaluated in the multidisciplinary epilepsy team of Tampere University Hospital during the consideration for VNS therapy. Before the VNS implantation surgery, patients undergo 3T MRI and FDG-PET -examinations regarding the epilepsy surgery evaluation; the possibilities for potentially curative epilepsy surgery are evaluated before initiating palliative neuromodulation therapy.

The AED therapy is optimized and a four-day video-EEG -examination is usually performed before the VNS surgery to assess the precise seizure onset zone, type of epilepsy and the seizure types. Patients also meet with a neuropsychologist and a psychiatrist, and the suitability for the VNS therapy is evaluated.

After the decision to proceed to VNS therapy has been made, the patient meets with an epilepsy nurse twice. Along with a discussion about practical questions, BDI (Beck's Depression Inventory) scale and Epitrack -tests are performed to assess the mood and cognitive status of the patient. The seizure diaries are analyzed and seizure

types settled. The focal aware and focal impaired awareness seizures are divided into two groups; disabling and non-disabling seizures. In VNS therapy, we concentrate on the treatment of disabling seizures.

4.2.7.2 Procedures after the implantation

The protocol for VNS device programming in Tampere University Hospital is based on original publications, own clinical experience and to the protocols of some VNS centers with high reputation: Lieven Lagae, University of Leuven, Belgium; Angus A. Wilfong, Texas Children`s Hospital, USA; Jeremy Slater, University of Texas HSC, USA; James Wheless, University of Tennessee HSC, USA and Sandra Helmers, Emory University School of Medicine, USA.

In our institution, the patients are followed up by the same nurse and the same epileptologist. On every outpatient clinic visit, the device is checked and the seizure diaries are analyzed. Normal mode and system diagnostics including lead impedance are tested. Also, all the stimulation settings are checked and the device information, including autostimulation activation logs, are saved for scientific research use, and for a patient follow-up to determine the level of responsiveness to the therapy. If there are problems with tolerability, the frequency can be lowered to 20 Hz or the pulse width can be lowered to 130 μsecs until the next visit.

The first visit after the surgery with the epilepsy nurse is after 2 weeks, and the device is started. The nurse informs the patient about the possible adverse effects. The first stimulations usually are the toughest, and if the patient suffers adverse effects, they are looked after for 20-30 minutes. If the VNS model 106 is implanted, the autostimulation detection is started with 0 mA stimulation. The heartbeat sensitivity setting is defined to achieve as accurate heart rate monitoring as possible.

After the first visit, patients meet with the epilepsy nurse every 1 to 2 weeks until the goal settings are reached; the output current is increased by 0.25 to 0.5 mA on every visit. Once the output current of 1.0 mA is reached, the autostimulation setting is initiated with a threshold rate of 40%. The target threshold is usually the most sensitive, 20%. The stimulation settings for automatic stimulations are usually the same as for normal mode stimulations.

After 3 months of VNS therapy with the target settings, the patients meet with the epilepsy nurse and the mood and possible cognitive symptoms are evaluated along with the possible adverse effects. Epitrack and BDI -tests are performed.

3 months after that visit, the patients meet with an epileptologist. The response to the VNS treatment is evaluated along with the antiepileptic medication. At this point, the stimulation cycle can also be enhanced.

After the epileptologist appointment, the patients meet with the epilepsy nurse in every 2 to 3 months. At this point also the nurse can alter the stimulation cycle if needed. Also, the Epitrack and BDI tests are executed again on the first follow-up visit.

After reaching 18 to 24 months of VNS therapy in total, patients meet with the epileptologist. The response to VNS therapy is evaluated again and the decision of the future is determined - if to continue with VNS treatment or to proceed to other treatment options. At this point, the output current can also be increased up to 2.0-2.5 mA and duty cycles of 30 / 48 seconds or 7 / 21 seconds can be tested.

When continuing with the VNS therapy, patients meet with the epilepsy nurse once in every 6 months and the epileptologist when needed, or usually at least once a year. At the nurse appointments, Epitrack and BDI tests can be executed, and the need for other treatment interventions are evaluated.

4.2.7.3 Possible inconsistencies in the follow-up

In most of the patients, the follow-up is very straightforward as described before. Although in some cases the protocol cannot be strictly followed, for example due to the following reasons.

4.2.7.3.1 Battery depletion

The battery is estimated to last for 6 to 8 years, although the used stimulation settings might affect the sufficiency of the battery substantially. When connecting the VNS device to the programming device, it indicates if the battery is near the end of service. In that case, the follow-up visits are actualized more frequently, once in every 3 months.

The effects of VNS therapy are evaluated comprehensively and the decision of the continuation of VNS therapy is made. The most common decision is to continue with VNS therapy, and at this point, the pulse generator is usually upgraded to a newer model which may entail new treatment modalities, such as automatic stimulation.

If the decision is to discontinue VNS therapy, one option in our center has been proceeding to ANT-DBS therapy. In some patients, the treatment of epilepsy has been continued conservatively.

4.2.7.3.2 High impedance situation

If encountering a high impedance (HI) situation, we first take a thorax x-ray image to rule out a mechanical breakage of the lead. If there is no clear reason for HI in the x-ray, the reason is most likely a scar formation around the nerve, requiring revision surgery.

At that point, the significance of VNS therapy on seizures, cognition, and mood is evaluated. If there is not clear efficacy, the current can be changed to 0 mA for 3 to 6 months to determine whether the VNS therapy had an effect or not. If there has been clear efficacy, we proceed to revision surgery. If there has not been satisfying efficacy, then the removal of VNS should be considered.

4.2.7.4 Stimulation settings

In our VNS programming protocol, we aim for the following stimulator settings.

Output Current: Starting with 0.25 mA. The OC is increased in 0.25 to 0.5 mA steps in every one or two weeks. In some cases, the increase could be done faster for example due to practical reasons. The target current is 1.75 mA depending on tolerance. The minimum target current is 1.0 mA.

Pulse Width: Starting with 250 μs. If there are problems with tolerability, temporary usage with 130 μs is also possible, but continuous stimulation with that setting is not recommended due to lack of efficacy. The magnet setting is 250 μs.

Frequency: Starting with 30 Hz. If there are problems with tolerability, it can be decreased to 20 Hz. It's also possible to start at 20 Hz.

Stimulation Cycle: Starting with 30 sec ON-time and 5 min OFF-time. After six months the stimulation cycle could be altered by shortening the OFF-time. If the efficacy is not satisfying, the cycling can be enhanced more, or if there are problems with tolerability, setting with a 7 s / 21 s cycle can also be tested.

Magnet stimulation: Starting with 60 sec ON-time. Pulse width 250 or 500 μs. Starting with 0.25 mA higher Output Current than with normal stimulation. If the patient does not feel the effect of magnet stimulation, the output current is increased

to 0.5 mA higher than normal stimulation. If having problems with tolerability, ON-time could be decreased to 30 or 14 seconds.

4.3 Statistical methods

In the first three studies, IBM SPSS Statistics software versions 20.0 and 23.0 were used to perform the statistical analyses. Microsoft Excel software was used in making other calculations and to build the figures. The box-plot figure of the second paper was as well built with SPSS.

Of the statistical tests, nonparametric Mann-Whitney and Kruskal-Wallis tests were utilized depending on the amount of the variables. In the third paper we also utilized the one-sample Wilcoxon signed rank test. All of the tests are applicable in small samples. In the fourth study, 95% confidence intervals were calculated and compared between groups. The classic approach for rejecting the null hypothesis is applied, whereas significance level, e.g. P-value is less than 0.05.

In the fourth study, the data were analyzed in Matlab (MathWorks, Natick, MA) using custom software. In the fourth study, in cases where statistical analysis was performed, 95% confidence intervals were calculated and compared between the groups.

5 RESULTS

5.1 Study I

Altogether in 10 (91%) patients out of the study population of 11 patients, the response patterns for consecutive VNS and ANT-DBS therapies were similar. All three patients that had a progressive response from VNS therapy, gained progressive response also from DBS therapy. Two patients that were considered partial responders to VNS therapy were also partial responders to DBS therapy. One of the nonresponders to VNS therapy had a progressive reduction in seizure frequency with ANT-DBS and the rest of the nonresponders for VNS, 5 patients, were also nonresponders to DBS therapy. Therefore, these results support our hypothesis of the association between the responses to VNS and DBS therapy.

A concept of "partial responder" is not widely acknowledged, although in our material several patients showed similar response patterns with an initial but not sustained response. Therefore we composed a separate group for these patients.

Averagely the patients' AED burden increased; at the beginning of the follow-up, the patients were averagely on 2.54 AEDs as at the end of follow-up on 2.91 AEDs.

High impedance incidence was quite high in our cohort (three out of eleven patients) which reflects our habit to consider other treatment options as an alternative to a lead revision surgery.

5.2 Study II

We were able to assess the reliable effect on seizure frequencies in 11 out of 14 patients. Of these patients, four out of eleven (36.4%) were responders with at least a 50% reduction in seizure frequency with the rVNS in comparison to the baseline. Five (45.5%) of them did not have a significant change and two (18.2%) of the patients showed a clinical decrease in seizure severity. One of the nonresponders reported reduced side-effects from stimulation with rVNS in comparison to VNS and none of them had more seizures after initiation of VNS with rVNS therapy.

We assessed the total amount of electrical charge, "VNS dose", delivered in patients with different VNS modalities. The total charge was significantly less with model 106 than with models 102 or 103 (p=0.001, Mann-Whitney test). The average charge (Q_{total}) for one day in VNS with rVNS therapy was 142.56mC and in traditional VNS it was 321.09mC. The mean decrease in Q_{total} was 178.5mC (ranging from -6.1mC to 422.7 mC, mean 178.5mC, and SD 140.7mC).

Moreover, the VNS programming protocol has advanced over time, and nowadays the target current is usually 1.75mA, whereas, in the past, the output current might have been unnecessarily high. Two of the patients did not have their normal mode stimulation settings altered and therefore the total charge also stood unaltered. The threshold rates with those patients were quite high and therefore the share of automatic stimulations was quite low, around 10% of the stimulations.

The AED treatment with the changes was assessed. Nine out of 14 (64%) patients did not experience any changes in their AED regimen. In five (36%) patients the changes made were mostly reductions. Also, for two patients an AED was initiated but later discontinued. Within the responder patients, two out of four experienced only AED reductions. Also, the two patients that experienced a decrease in their seizure severity did not experience any alterations in their AED regimen.

5.3 Study III

The total dataset of 208 SPs of 30 patients was analyzed. The duration of a single SP ranged from 1 to 352 days (mean 71, SD 57 days). A patient had averagely 6,93 SPs (range from 1 to 12). The cumulative follow-up time for stimulation related analysis for all patients combined was 14778 days, i.e. more than 40 years. Individual follow-up time for a patient varied from 13 to 999 days.

The largest number of SPs was with 5 minutes OFF-time (n=146) compared with 30, 17 and 15 SPs with 3min, 1,8min, and 1,1min OFF-times, respectively. All new implantations had the majority of SPs with 5-minutes OFF-time (80%), whereas in replacement group 56% of the SPs with 5-minutes OFF-time. MFE patients only included 5-minutes OFF-time, whereas in TLE 56%, and in ETLE 52% of the SPs were in this group.

First, we analyzed whether the threshold rate and epilepsy type have an effect on the frequency of autostimulations. The threshold rate had a major effect on the number of autostimulations (p = 0.000). The averages of daily autostimulations in all patients in the different threshold groups were the following: threshold 20%:

163.4; 30%: 78.8; 40%: 55.7; all thresholds: 99.3. The patients with TLE (mean: 103.1) and MFE (mean: 111.1) received the largest number of autostimulations whereas patients with ETLE (mean: 78.6) received less. This finding was the most pronounced with a threshold rate of 20%. When the settings affecting the number of stimulations were fixed by exclusion (OFF-time 5min, ON-time 30sec, threshold 20%), the difference between ETLE and other groups was significant ($p = 0.001$) whereas TLE and MFE groups were similar ($p = 0.487$).

Second, we analyzed how altering the stimulator settings affect the number of stimulations and total charge (Q_{total}). In the analysis we included only the SPs with comparable stimulator settings; Output current 1.75mA, Frequency 30Hz, Pulse width 250μs, ON-time 30 seconds and the threshold for automatic stimulations 20%. When OFF-time was shortened, Q_{total} ($p<0.0005$), number of autostimulations ($p=0.002$) and normal mode stimulations ($p<0.0005$) increased as the share of autostimulations ($p<0.0005$) decreased. When comparing rVNS and traditional VNS (computational) total stimulation counts in different OFF-times, the differences were also significant ($p<0.0005$). Usage of rVNS increased the total amount of stimulations and Q_{total} if the rest of the settings stood unaltered.

Third, when comparing all SPs with 5-min OFF-time, the difference between thresholds 40% (57 SPs) and 20% (40 SPs) was assessed. The lowered threshold increased the number of autostimulations by 277% and decreased the number of normal stimulations by 24% while increasing the total stimulation count by 27% ($p < 0.0005$).

All the patients were simultaneously treated with AEDs, approximately 3.03 (SD 0.81) AEDs at the beginning of the follow-up, and approximately 2.83 (SD 0.79) AEDs at the end of the follow-up. A major part of the patients (16, 53.3%) did not experience any changes in their medication. Eight (26.7%) of the patients experienced only reductions, two (6.7%) only increases, and four (13.3%) reductions and increases.

5.4 Study IV

A total of 447929 autostimulation timestamps (average/patient 12106, median/patient 12977, range 658 to 21946 stimulations per patient) were analyzed. The data was downloaded from the VNS devices of 30 patients consisting of 167 stimulation periods.

There was a clear circadian pattern in autostimulation activations that was not dependent on the threshold rate. When the data was analyzed in seizure clusters, the cluster profiles in all three threshold rates were similar. Autostimulations occur the least often during the night, the number increased substantially in the morning, the finding is statistically significant ($p < 0.05$). The patterns are similar in TLE and MFE patients. In patients with prior VNS therapy, the peak in stimulation clusters during the morning hours trended to be more prominent, although the difference was not statistically significant. ETLE patients show a similar trend, although the data is too distributed for conclusions.

Within battery replacement and new implantation rVNS patients, the rVNS activation profiles are similar; in patients with prior VNS therapy, the peak in stimulation clusters during the morning hours trended to be more prominent, but the finding was not statistically significant.

6 DISCUSSION

Epilepsy is the most common of the neurologic diseases concerning an ample amount of people worldwide; either the patients themselves or the families of the people with epilepsy, as well as having extensive economic influences (Banerjee et al., 2009). The negative effects caused by epilepsy are remarkable. Epilepsy is usually a life-lasting disease, requiring often hundreds or even thousands of visits to healthcare services, and sometimes even intensive care due to traumas caused or status epilepticus episodes. Some of the patients lose their ability to work or to live without constant care.

The majority of epilepsy patients achieve satisfying responses with one or two antiepileptic drugs. However up to 30% of the patients are medically refractory, i.e. the sustained seizure freedom is not achieved with two tolerated, appropriately chosen and used antiepileptic drug schedules (Kwan et al., 2009). This group of patients leads to the biggest burden for healthcare services. Epilepsy surgery would be the primary treatment option for these patients, but it's not feasible for all the patients.

Therefore, nowadays, the treatment options for epilepsy are not sufficient and it is necessary to develop new and to improve the existing treatment options for refractory epilepsy. Today, the most intriguing option is by neuromodulation therapies - along with deep brain stimulation and intracranial responsive neurostimulation, the vagus nerve stimulation has shown promising results in the patients that do not gain seizure control with AED therapy alone.

6.1 Discussion of the results

6.1.1 Association between the responses to VNS and DBS treatments

According to our first study, there are similarities between the responses to VNS- and ANT-DBS- therapies in refractory epilepsy patients: in 10 out of 11 patients

(91%), the response was similar, therefore we can propose the response of prior VNS predicting the response to subsequent ANT-DBS.

The number of studies including patients with both of these therapies is limited. In the SANTE trial (Fisher et al., 2010) there was a subgroup of patients with prior VNS. In the follow-up data of that trial (Salanova et al., 2015) the median seizure reduction with the group of prior VNS therapy and without prior VNS therapy, was 69% in both of those groups. The reasons for VNS discontinuation were not reported, thus the patients can be assumed to be nonresponders for VNS. Therefore this data does not support our results. This discrepancy may reflect the different nature of the populations in these studies; some of the VNS patients might have had some response to the therapy but they are considered as nonresponders, and VNS patients with a good response were not included in the study. In our study, the patients are not selected by such rigorous assessments, as they are ordinary patients treated in our center in everyday clinical practice, and the data is gathered retrospectively without the study affecting the treatment. Park et al. (2019) recently published results of seven patients with previously failed VNS therapy. Five out of these patients (71.3%) were responders to ANT-DBS therapy. This discrepancy to our results may be due to different inclusion criteria and treatment paradigm with ANT-DBS -therapy (Park et al., 2019).

There are some neurobiological findings that may explain the similarities between the responses; VNS seem to excitate the cerebral blood flow in thalamic structures forming a conclusion that the thalamus is consistently involved in VNS therapy (Ko et al., 1996, Henry et al., 1998, Henry et al., 1999, Ben-Menachem, 2002).

In the first study, in all VNS responder patients, the VNS therapy was discontinued; in one case, the efficacy was not thought to be sufficient, in one patient the battery depleted and in one patient, there was a high impedance situation. One may question the ethics of discontinuation of a working therapy. In every case, the decision was made according to the assumption of best possible treatment option and together with the patient.

The current results of the association between the responses to subsequent VNS and ANT-DBS therapies do not unambiguously determinate, if proceeding to ANT-DBS therapy after failed VNS therapy might lead for favorable responses, or which patients may benefit of the change.

6.1.2 Electrical charge needed decreases when using rVNS

In our second study, inititation of rVNS in VNS therapy led to decreased electrical charge, "VNS dose", delivered to the patients, that occurred due to altered normal mode stimulation settings, which we were able to perform due to an additional seizure control gained with rVNS; prolonged OFF-time and decreased stimulation intensity parameters. In 13 out of 14 patients, the initiation of rVNS increased the total number of stimulations, and in 12 out of those 13 patients, the Q_{total} decreased.

Reduced power usage would potentially lead for prolonged battery life, thus potentially reduced surgeries and lesser risk of surgery-related complications. Prolonged battery life would improve the cost-effectivity of the treatment.

Some side-effects are associated to the used stimulation parameters and reducing the stimulation intensity may reduce the side-effects.

6.1.3 Responder rates

We included the seizure frequency information in the first two studies.

In the first study, we included 11 patients. Only 3 out of 11 patients (27.3%) were considered as progressive responders for traditional VNS therapy. We also had 3 patients considered as "partial responders", with no sustained reduction of seizures by at least 50%, which may also reflect the fluctuating nature of epilepsy. Our responder rate is fairly low compared to the other studies, which is due to the study population: we included only the patients with the decision to discontinue the VNS therapy, thus this number does not represent the real responder rate in our institution. In the prior efficacy studies, 30-60% of the patients are considered as responders for traditional VNS. (Ryvlin et al., 2014, Cukiert, 2015, Elliott et al., 2011).

In the second study, we compared a newer model of VNS with rVNS to an older model of VNS - therefore the response to the traditional VNS therapy cannot be assessed, all of the patients are considered as responders since the decision to continue with the VNS therapy has been made. The additional responder rate with rVNS was 36.4% (4 out of 11 patients) during the follow-up, which is slightly less than in a large study of 113 patients with a follow-up of three years (Hamilton et al., 2018). They had 62 patients with former VNS with a responder rate of 71%.

Our results support the findings of VNS response improving progressively over time (Englot et al., 2016, Révész et al., 2018, Wang et al., 2019). In the results of the first study, the similar response pattern is apparent. Three out of eleven patients were

responders, and the response improved over time. In the results of the second study, in three out of four patients the response improved over time.

The AED treatment with the changes was assessed in the studies including the response analysis. In the first study, averagely the patients' AED burden increased. According to our evaluation basing on the clinical observation during the clinical practice, we don't believe that the changes in the AED regimen would explain the responses. In the second study, within the responder patients, two out of four experienced only AED reductions. Also, the two patients that experienced a decrease in their seizure severity did not experience any alterations in their AED regimen. Thus, with the initiation of rVNS, better seizure control was not related to the changes in AED therapy.

6.1.4 Number of autostimulation activations

The majority of the published research articles do not include the number of autostimulation activations.

Boon et al. (2015) presented the following numbers for automatic stimulation activations in different threshold rates; 70% 0.64/h, 60% 0.89/h, 50% 1.39/h, 40% 2.35/h, 30% 4.37/h, and 20% 8.25/h. Lowering the threshold from 40% to 20% increased the number of activations 3,51-fold. Fisher et al. (2016) reported the nonseizure-related autostimulation activations increasing over sevenfold when decreasing the threshold for automatic stimulations from 40% to 30%.

In our third study, the automatic stimulation activations in all patients were the following; 40% 2.32/h, 30% 3.28/h, and 20% 6.81/h. Lowering the threshold from 40% to 20% increased the number of activations 2.94-fold. Our results show a similar tendency to the results of Boon et al. (2015) and Fisher et al. (2016).

Fisher et al. (2016) reported the therapy time increasing from 10% to 10.6-15.9% after the initiation of autostimulation. In our results of the third paper, we propose that the increase in autostimulation activations is more dependent on the OFF-time. The additional effect on the number of total stimulations on different OFF-times was the following; 5min +57%, 3min +42%, 1.8min +7%, and 1.1min +2%. Our results support the previous finding that the initiation of autostimulation increases the therapy time.

6.1.5 Circadian distribution of autostimulations

The circadian rhythmicity of autostimulations in VNS therapy has not been assessed previously. Our findings in the fourth study suggest that the circadian distribution of automatic stimulations resemble the circadian rhythmicity of cortisol secretion, e.g. the autostimulation occurrence peaking in the time of morning wake-up.

We were not able to compare circadian occurrence of autostimulation clusters to the seizure occurrence. Therefore, our findings of autostimulation cluster occurrence may relate to non-seizure related aspects, e.g. circadian fashion of autonomic functions and sleep-wake cycle rather than epileptic seizures

Although, seizure frequency has been proved to occur in a similar circadian trend to cortisol secretion (van Campen et al., 2015) and especially temporal-lobe and frontal-lobe onset seizure occurrence show circadian patterns. However, despite some results, those occurrence patterns are not clearly emphasized in the morning (Nzwalo et al., 2016, Pavlova et al., 2004, Loddenkemper et al., 2011, Ramgopal et al., 2014, Zarowski et al., 2011, Spencer et al., 2016, Anderson et al., 2015, Duckrow et al., 2007).

Also, the associations between stress and epileptic seizures are well known, and it may be partly related to the serum cortisol concentration (Goodman et al., 2019, Gunn and Baram, 2017, van Campen et al., 2016, Majoie et al., 2011, Zobel et al., 2004).

We suggest that the autostimulation clusters do not only reflect the seizure occurrence but also the physiological and pathological autonomic functions of the body that show circadian fluctuation. Concurrent autonomic dysfunction is known to be present in patients with refractory epilepsy. Also, the risk of sudden cardiac death is increased in the morning. (Muller et al., 1987, Bardai et al., 2012, Verrier et al., 2020).

It has been hypothesized, that the shift from constant cyclic stimulation to more variable stimulation patterns would lead for better response over time. In the results of the third study, longer OFF-time led for a larger share of autostimulations, that may lead for better long-time outcomes.

6.1.6 Seizure onset zone and autostimulations

In our results, the temporal lobe (TLE) and multifocal (MFE) onset seizures tend to activate autostimulation more often than extratemporal lobe (ETLE) onset seizures. In circadian variation of the autostimulation cluster occurrence, the morning peak

was clearly visible in TLE and MFE patient groups, and the dispersion in ETLE group was wider – although the patient group was too heterogeneous for any conclusions.

As seizures that onset from different zones activate different neural networks, have differences in cardiac manifestations and occur in different circadian patterns, the varied behavior of autostimulations is justifiable.

In our study, the material was too small and heterogeneous for outcome analysis in regard of the seizure onset zone. In the study of Elliott et al. (2011), mean reduction in seizure frequency was more evident in TLE (74.6%) compared to bitemporal (62.8%), FLE (64.3%) or MFE (53.8%) seizures, but the differences were not significant. The rest of the outcome-related papers cited in this book do not address the effect of seizure onset zone on the outcome or behavior of automatic stimulations (Boon et al., 2015, Fisher et al., 2016, Ryvlin et al., 2014, Cukiert, 2015, Englot et al., 2016, Révész et al., 2018, Wang et al., 2019).

6.2 Limitations of the study

The sample size of this study was relatively small. In the first paper, we included 11, in the second 14, and in third and fourth papers 30 patients. Due to the overlapping of the study populations, altogether 42 patients were included. In addition to the relatively small study population, the patients were quite heterogeneous as seen in Table 5. Therefore the study settings were not well powered for outcome or patient characteristic related analysis even though follow-up times were quite long in some cases.

Since the responsibility for the follow-up of the seizure frequencies lay on the patients, due to human factors, the follow-up data might not be accurate. Also, during VNS therapy, all of the patients receive simultaneous AED therapy, possibly corrupting the results regarding the response. The effect of AED therapy was evaluated in every study. The conclusions were, that the effects of AED therapy on the outcome results were minor.

The study designs were retrospective register studies, therefore, in order to return the values for selected variables the interpretation of patient files is necessary and more sensitive for bias. Prospective controlled studies with larger groups of homogeneous patients would produce results with better quality.

Previously to VNS being an established treatment option in our institution, we did not have a protocol for the usage of VNS. Since the target settings and

programming scheme varied, the comparability of the patients was not very comprehensive. This limitation applies to the first two studies.

6.3 Patient selection for VNS therapy

Careful and comprehensive patient selection for VNS therapy could lead to better treatment results and reduced costs for society. If the prediction of the outcome will be more reliable, the therapy should be allocated for the patients with a good prognosis.

Along with the prognosis, the individual factors of the patients should be considered. The evaluation of the severity and the disability of the seizures are already included in our VNS protocol.

In patient selection, other effects of VNS could be taken into consideration; in some cases VNS might have efficacy on several diseases simultaneously. VNS has been proven to have fairly good efficacy on depression (Roosevelt et al., 2006, Carreno et al., 2017, Müller et al., 2017), and it also has approval by the FDA in the treatment of obesity, although the efficacy still remaining unclear (Val-Laillet et al., 2010, Pelot and Grill, 2018). VNS therapy might also have a positive effect on several other pathologies, such as traumatic brain injuries, rheumatoid arthritis, Crohn's disease and fibromyalgia. (Neren et al., 2016, Bruchfeld et al., 2010, Lange et al., 2011, Bonaz et al., 2016, Koopman et al., 2016).

6.4 Timing of VNS implantation

In our center, the VNS is often implanted in a fairly late phase of the epilepsy disease. We included the information about the duration of epilepsy in the data of the third cohort (third and fourth paper). In these 30 patients, the mean duration of epilepsy before VNS implantation was 23.8 years (SD 11.70 years), ranging from 5 to 48 years. Therefore, early diagnosing of refractory epilepsy and early evaluation for VNS therapy might lead for better outcome.

If the VNS would be implanted earlier, the duration of VNS therapy would be longer, leading for a better outcome; due to earlier implantation (Wang et al., 2019) and due to longer period of VNS therapy (Englot et al., 2016, Révész et al., 2018, Wang et al., 2019). The initial expenses in VNS therapy are substantial, but the cost-effectivity of the therapy has been established. It might lead to reduced visits to

healthcare services, fewer accidents and status epilepticus episodes. Therefore the net effect could be economically positive, not to mention the effects on the seizures and the quality of life. (Boon et al., 2002, Banerjee et al., 2009, Jennum et al., 2016, Kopciuch et al., 2019, Martorell-Llobregat et al., 2019).

6.5 Options when VNS is not effective

As described before, approximately a half of the patients are nonresponders. Less than 10% of patients achieve complete seizure freedom (Englot et al., 2016).

If the satisfying response is not achieved, the VNS therapy should not be discontinued too soon since the response improves over a longer period of the therapy (Englot et al., 2016, Révész et al., 2018, Wang et al., 2019). Enhancing the device settings and altering the duty cycles might have an effect on the seizure counts and severities.

Refractory epilepsy patients are usually treated with antiepileptic drugs despite ongoing VNS therapy. AED therapy can be used and altered regardless of VNS. Initiating new AEDs for refractory epilepsy patients might improve the seizure situation, but the prognosis is not too flattering (Mohanraj et al., 2006, Luciano et al., 2007). In some patients, the seizures are related to external factors such as stress or menstruation cycle; an intervention on these factors might improve the seizure situation substantially (van Campen et al., 2015, Maguire and Nevitt, 2019).

Simultaneous VNS and DBS therapies are possible, although there is not a lot of experience. Franzini et al., (2009) implanted the same patient with both DBS and VNS in a patient with chronic cluster headache, without any side effects. The results of simultaneous VNS- and DBS- therapies have not been reported in epilepsy patients. In our first study, one patient implanted with subsequent ANT-DBS after VNS, did not have the VNS system explanted. Approximately after a year of ANT-DBS-therapy, the VNS system was turned on again. The patient did not suffer any additional side effects.

All the VNS patients in our institution undergo an evaluation for epilepsy surgery prior to VNS implantation, and some of the patients have gone through epilepsy surgery procedures. Present VNS therapy is not a contraindication for epilepsy surgery, thus re-evaluation for the epilepsy surgery might be a considerable option.

Alternative treatment options for refractory epilepsy, for example, ketogenic diet, are possible to initiate during the VNS therapy. Also, the association between VNS and neurotransmitter and hormonal systems of the human body offers an intriguing

field for future research. For example, the effects of VNS are partly mediated by norepinephrine and serotonin systems in the brain. There is no research concerning the effect of SNRI (serotonin-norepinephrine reuptake inhibitor) medication as an adjunctive treatment with VNS for epilepsy or depression.

Moreover, the association between corticosteroid system and epilepsy is undisputed and manipulation of the HPA (hypothalamic-pituitary-adrenal) system might affect the outcome. Already, for example, ACTH therapies have shown some efficacy in refractory epilepsy. (Gobbi et al., 2014, Inui et al., 2015). Cortisol levels are proposed to be elevated in refractory epilepsy patients and the levels reduced by VNS therapy (Majoie et al., 2011). This unbalanced situation is probably mediated by impairment in the negative feedback system of the hypothalamic-pituitary-adrenal axis (Zobel et al., 2004). As the peak in cortisol concentration seems to decrease the seizure threshold and its metabolites to increase it, stabilization of the corticosteroid system might have positive efficacy on epilepsy patients (van Campen et al., 2016, Perez-Cruz et al., 2007).

6.6 VNS protocols

In Tampere University Hospital a new protocol for the treatment of VNS patients was initiated a few years ago, described in detail in chapter 4.2.7. A clear protocol should be established in every institution, to provide equal and evidence-based treatment for every patient. A protocol-based treatment forms a distinct scheme, making the follow-up and the basis for scientific researches easier.

In most of the studies, the VNS protocol is not elucidated. Typically, only the presurgical evaluation is explained, usually including v-EEG, MRI and SPECT examinations. In the E-37 study (Fisher et al., 2016) the baseline evaluations included the following questionnaires; the Quality of Life in Epilepsy-Patient-Weighted; QOLIE-31-P for subjects 18 years and older, Seizure Severity Questionnaire (SSQ), and the National Hospital Seizure Severity Scale, NHS3. In our protocol, the BDI (Beck's depression inventory) and Epitrack (for cognitive functions) tests are performed. The seizure types and severities are evaluated in our center according to the video-EEG records and the seizure descriptions given by the patients and eyewitnesses. The BDI includes a notable part of the QOLIE-31-P -questionnaire. In our protocol, we do not have a questionnaire concerning the quality of life.

6.7 Possible negative effects on patients

The conventional adverse effects and complications of VNS therapy are described in detail in chapter 2.2.8. In addition to these drawbacks, VNS therapy might cause harm in patients with several other mechanisms.

The VNS pulse generator is a foreign body, that the patients can feel and possibly see on the upper chest. It is working around the clock and some of the patients feel every single one of the stimulations over the course years, possibly causing a negative effect on the quality of life. The visible pulse generator might emphasize the stigma caused by epilepsy. Some patients are disturbed by the pulse generator, and the "twiddler's syndrome" might lead to device-related late complications (2.3.3.2). Due to these reasons, to avoid excessive problems, the mental state and the mood should be assessed before the initiation of VNS therapy, and during the follow-up.

Even though the adverse effects of VNS therapy usually withdraw over time, they may sustain. For example, in some patients, the hoarseness caused by the stimulation might cause embarrassment and social problems. The patients are equipped with a magnet that they can also use to stop the activity of the stimulator. Some of the patients may misuse this option by stopping the stimulator for too long a time, leading to a greater risk of seizures.

Traveling with a VNS should be trouble-free, but the patients are recommended to carry a VNS patient card on them in case of problems. The airport security systems should not interfere with the VNS device. The family and friends of a VNS patient should be aware of the disease and the stimulator, to be able to take action adequately in case of a seizure. The effects of external defibrillation on the VNS device are unpredictable. A case report of successful resuscitation including defibrillation led to no malfunctions in the VNS device (Wittstock et al., 2018).

6.8 The future of the VNS

The newest model of VNS, SenTiva is the smallest and lightest of all VNS devices introduced. It has all the properties of VNS model 106 AspireSR, with a novel options for scheduled programming, and for detection of a patient's posture. Therefore the need for outpatient clinic visits is reduced, and the stimulation settings may be dependent on the time of day. For example, some of the patients experience seizures only during the night.

The particulars of the VNS therapy are continuously under research and new ways to improve this treatment option are being developed. The improvement in VNS devices may lead for even better responses in VNS-treated patients in the future along with a better selection of patients, timely initiation of VNS therapy and improved programming of the device.

7 CONCLUSIONS

The conclusions of the four original research papers are the following.

1. There are similarities in the responses for consecutive VNS and ANT-DBS therapies.

2. The initiation of automatic stimulation in VNS therapy leads to a better seizure outcome in one third of refractory epilepsy patients.

3. The initiation of autostimulation might allow the reduction of stimulation intensity related settings, leading to lesser power usage.

4. Shortening the OFF-time and lowering the autostimulation threshold leads to a significantly increased amount of stimulations.

5. Epilepsy type might have an effect on the function of autostimulation activations.

6. The circadian pattern of autostimulation activations resembles the pattern of cortisol concentration.

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PUBLICATIONS

I	Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy
II	Autostimulation in VNS treatment: modulating neuromodulation
III	Frequency of automatic stimulations in responsive vagal nerve stimulation in patients with refractory epilepsy
IV	Circadian distribution of autostimulations in rVNS therapy in refractory focal epilepsy patients

PUBLICATION I

Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy

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ORIGINAL RESEARCH

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Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy

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Abstract

Objectives: Neurostimulation has offered new treatment options in refractory epilepsy, first with vagus nerve stimulation (VNS) and more recently with deep brain stimulation (DBS). There is a lack of previous detailed data assessing the relationship between VNS and ANT-DBS. The aim of this study was to investigate the potential correlation between therapeutic responses to VNS and ANT-DBS.

Materials and Methods: A total of 11 patients with previous VNS therapy underwent ANT-DBS implantation. Monthly seizure counts starting from baseline before VNS extending to long-term DBS treatment were analyzed. The reasons for VNS discontinuation were assessed.

Results: Altogether in 10 of 11 patients, the response to VNS seemed to be similar to the response to DBS therapy. Progressive response to VNS was likely to correlate with a progressive response to DBS in three of three patients. Partial response to VNS was associated with a fluctuating response pattern to DBS in two patients. Five of six nonresponders to VNS were also nonresponders to DBS. One of the VNS nonresponders obtained progressive response to DBS.

Conclusions: This is the first study to evaluate in detail the effect of both VNS and ANT-DBS in refractory epilepsy patients. There is a putative association between VNS and DBS responses suggesting the need for further studies.

KEYWORDS
deep brain stimulation, epilepsy, follow-up, seizure, vagus nerve stimulation

1 | INTRODUCTION

Patients with refractory epilepsy comprise approximately 30% of all patients with epilepsy (Kwan & Brodie, 2000). Resective surgery is the treatment of choice for this patient group with focal epilepsy, but only 10-30% of patients are eventually amenable for surgery. Optimizing the pharmacological treatment can make some of these patients seizure free (Liimatainen, Raitanen, Ylinen, Peltola, & Peltola, 2008), but possibilities for major improvement with antiepileptic drug (AED) therapy are limited. Neurostimulation has offered new treatment options in refractory epilepsy, first with vagus nerve stimulation (VNS) and later with deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT).

VNS delivers an electrical current to the 10th cranial nerve via electrode, wrapped around surgically the exposed vagal nerve. Currently, VNS devices are being implanted in patients with refractory seizures who cannot have resective surgery or who have had surgery with poor results. Moreover, many of these patients have been treated with several antiepileptic drugs before receiving VNS implants (Ben-Menachem, 2002). The biological mechanisms causing

TABLE 1 Patient characteristics

No.	Sex	Age At VNS implant	MRI	Etiology	Seizure onset zone	Duration of VNS therapy	VNS responder	Reason for VNS discontinuation	DBS responder
1	M	18	Normal	Encephalitis	Multifocal	4 years 2 month	Yes, progressive	Battery depletion	Yes, progressive
2	F	17	Fronto-parietal bilateral gliosis	Encephalitis	Multifocal	4 years	Yes, progressive	Not effective enough	Yes, progressive
3	M	34	Bilateral perisylvian polymicrogyria	CD	Multifocal	5 years 3 month	Yes, progressive	High impedance	Yes, progressive
4	F	20	Bilateral perisylvian polymicrogyria	CD	Multifocal	5 years 1 month	Yes, partial	Lack of sustained efficacy	Yes, partial
5	M	24	Occipital bilateral heterotopia	CD	Multifocal	5 years 2 month	Yes, partial	Lack of sustained efficacy	Yes, partial
6	M	49	Normal	Unknown	Left temporal	6 years 6 month + 9 month and still ON	No	DBS implant, VNS not removed	No
7	M	42	Bilateral perisylvian polymicrogyria	CD	Multifocal	3 years 4 month	No	Lack of efficacy	No
8	M	19	Normal	Encephalitis	Left frontotem-poral	3 years 8 month	No	Lack of efficacy	No
9	M	17	Normal	Encephalitis	Multifocal	2 years 8 month (2 m break)	No	Lack of efficacy	No
10	M	38	Normal	Unknown	Frontal lobe, side unknown	4 years 3 month + 1 years 7 month	No	Lack of efficacy	No
11	F	29	Right hemi- megalenceph-aly	CD	Right frontotem-poral	4 years 9 month	No	Lack of efficacy	Yes, progressive

the effects of vagus nerve stimulation are still not fully understood (Roosevelt, Smith, Clough, Jensen, & Browning, 2006). VNS has been reported to reduce seizure frequencies by more than 50% in a group of patients with refractory epilepsy ranging from 30% (Ryvlin et al., 2014) to 50% (Cukiert, 2015).

Deep brain stimulation is a promising treatment choice for refractory focal epilepsy showing sustaining efficacy and safety (Salanova et al., 2015). DBS delivers currents directly to the ANT via electrodes implanted using stereotactic neurosurgical technique. The most optimal stimulation site is not unambiguously defined at this moment, and detailed anatomical variation of electrode location may have an effect on the outcome (Lehtimäki et al., 2016; Möttönen et al., 2015).

There is some evidence suggesting common pathways between VNS and ANT-DBS therapy. In VNS, there are synaptic connections from the nucleus tractus solitarius to higher centers in the brain including thalamus (Rutecki, 1990). Furthermore, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) of the effects of VNS in human beings have confirmed the influence of the vagus nerve on higher brain structures (Ko et al., 1996). These data suggest that the thalamus is consistently involved in VNS therapy.

The scientific basis for rational selection between different neuromodulation therapies is lacking. First, in the SANTE trial there was a subset of patients with previous VNS and/or resective surgery, but no predictive association with DBS was reported (Fisher et al., 2010). Second, there are no follow-up studies evaluating the modification from VNS to DBS (or vice versa). Third, the comparison between the efficacies of these treatment modalities has been challenging as there are only case reports about patients with both VNS and DBS implanted (Franzini et al., 2009).

To our knowledge, this is the first study comparing in detail the long-term results of VNS and DBS therapy. Eleven patients with previous VNS therapy later underwent ANT-DBS. Monthly seizure counts from the baseline before VNS to long-term DBS treatment were analyzed.

2 | MATERIALS AND METHODS

A total of 11 patients with previous VNS were implanted with ANT-DBS in Tampere University Hospital, Tampere, Finland, for refractory epilepsy. The VNS surgeries were performed in 2005-2011 and DBS in 2010-2013. All patients had been evaluated using inpatient video-EEG (electroencephalography) telemetry, 18-F-FDG-PET (fluorodeoxyglucose–positron emission tomography), and 3T MRI (3 Tesla magnetic resonance imaging) to identify potential epileptogenic zone/epileptic syndrome and evaluated for resective surgery. Clinical features of the patients are summarized in Table 1. The Study Plan was approved by the Ethical Committee of Tampere University Hospital, Tampere, Finland.

VNS was implanted microsurgically by exposing carotid sheath and the left vagus nerve, located medial to the jugular vein. A coil electrode (Cyberonics, USA) was wrapped around the vagus nerve, and the lead was fixed utilizing silicon anchors as recommended by the manufacturer. An internal pulse generator (Cyberonics) was implanted to the subcutaneous upper chest. From 10 of 11 patients, the VNS device was surgically removed before the implantation of DBS. DBS leads (3389, Medtronic) were stereotactically implanted bilaterally under general anesthesia using visual targeting based on 3T MRI STIR (Short Tau Inversion Recovery) images (Lehtimäki et al., 2016; Möttönen et al., 2015). An internal pulse generator (Activa PC, Medtronic, USA) was implanted to the subcutaneous upper chest. DBS was started within few days after surgery.

The period of effective VNS therapy was defined as a successful delivery of significant therapeutic currents. The effective VNS therapy could be terminated by turning the current OFF, depletion of the battery, or with a high impedance situation. The reasons for VNS discontinuation were re-evaluated. The varying VNS stimulation parameters were programmed individually to reach the best clinical outcome, the mean VNS settings at the end of the follow-up being the following: output current 2.1 mA, cycle 28.5 s ON / 66.5 s OFF, frequency 30 Hz, and pulse width 500 μs. The mean DBS settings at the end of the follow-up were the following: voltage 5.8 V (left), 5.3 V (right), frequency 147.3 Hz, pulse width 124.5 μs, and cycle 1 min ON / 5 min OFF. The programming of the DBS electrodes was planned according to MRI imaging.

The number of seizures during the year prior to VNS operation and afterward was evaluated from the patient records retrospectively for the majority of patients. For five patients, the original seizure diaries were possible to obtain for seizure counting for the entire time period. The response to the stimulation is considered as "yes" if there is a decrease of more than 50% in the total number of seizures (6 months average seizure count in any time point with effective stimulation) compared to the baseline (12 months average seizure count before VNS/DBS implantation). A progressive VNS responder is defined as a patient with continuous progressive decline in seizure frequency during effective VNS therapy. A partial VNS responder is defined as a patient with an initial >50% decrease in seizure frequency but with fluctuating seizure count over long term. A progressive DBS responder is defined as a patient with continuous progressive declination in seizure frequency during effective DBS therapy. A partial DBS responder is defined as initial >50% decrease in seizure frequency but with fluctuating seizure count over long term. A nonresponder to VNS or DBS is defined as less than 50% decrease in seizure frequency over the course of neurostimulation therapy. The patients having "partial response" cannot be considered as true responders as the effect does not sustain. We also briefly assessed the changes in drug treatment in every patient.

3 | RESULTS

Altogether in 10 patients of 11 (91%), VNS response was similar to the response pattern to DBS therapy. Three of 11 patients were

stable responders to VNS therapy. All these patients showed also progressive response to DBS therapy. Two patients had an initial response to VNS therapy that was not sustained over the course of years. All these patients demonstrated a partial response to DBS therapy. Six patients did not have satisfying effects by VNS based on the total number of seizures, and five of these patients did not have a response neither to DBS therapy. Only in one nonresponder to VNS therapy, there was a progressive response to DBS therapy. The details of seizure counts are shown in Figure 1 and patient characteristics in Table 1.

At the time of the VNS initiation, three of the patients were on AED monotherapy, one patient on two AEDs, five patients on three AEDs, and two patients on four AEDs, 2.54 AEDs on average. Subsequently, while proceeding to DBS therapy, three patients were on AED monotherapy, none of them on two AEDs, six patients on three AEDs, one patient on four AEDs, and one patient on five AEDs. At the end of follow-up, they were on 2.91 AEDs on average; one patient was on AED monotherapy, two patients on two AEDs, five patients on three AEDs, and three patients on four AEDs. During the VNS therapy, seven new AED introductions were enacted, along with

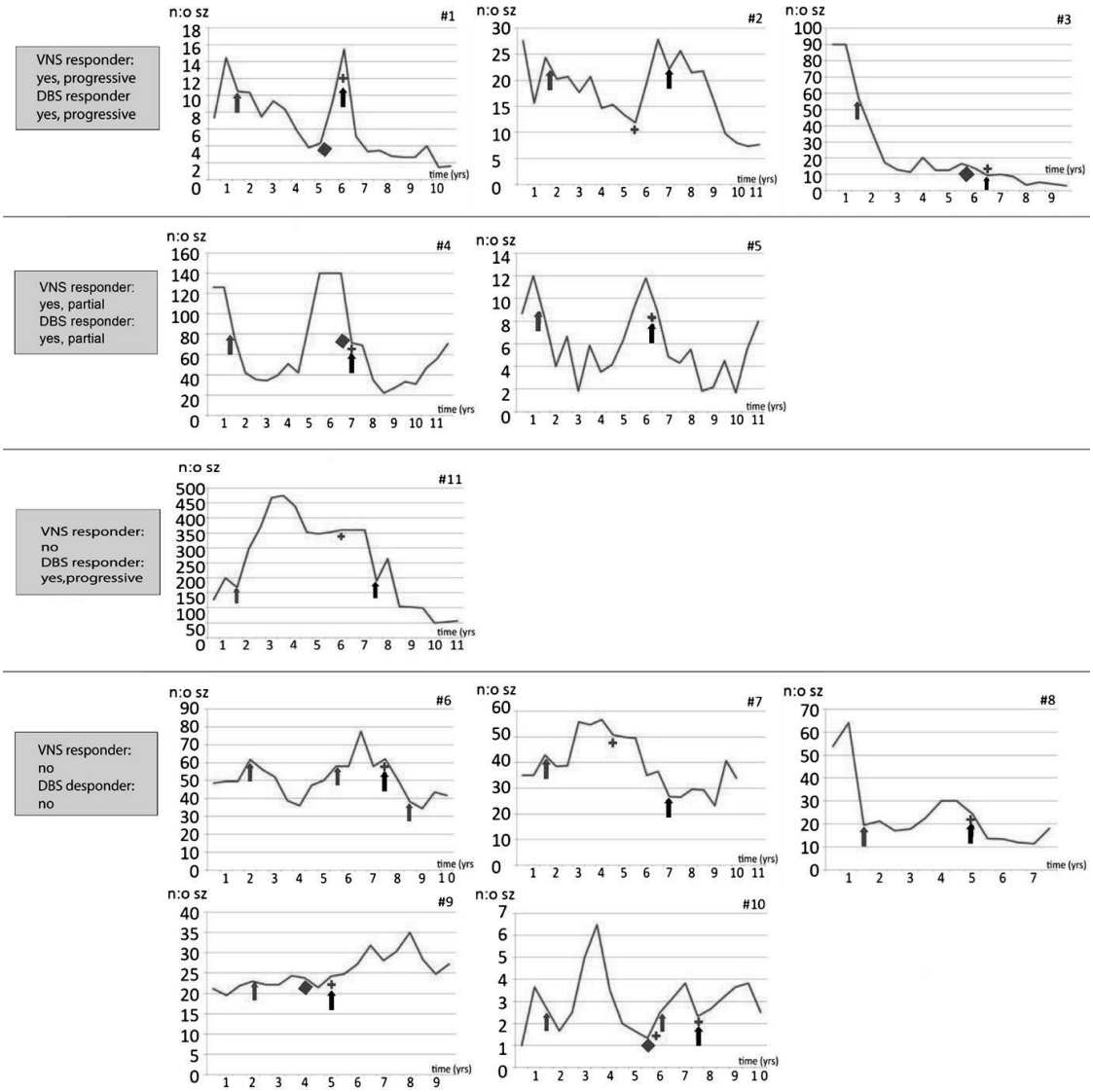

FIGURE 1 Mean monthly seizure count in six-month intervals. Legend: red arrow: VNS ON, red star: VNS OFF, red diamond: VNS high impedance in patients 3, 4, and 9, and battery depletion in patients 1 and 10, black arrow: DBS ON. Note: patient #6, second red arrow represents VNS battery change

the five increases in dosage, six decreases in dosage, and five discontinuations. During DBS therapy, seven new AED introductions, five increases, three decreases, and six discontinuations were executed. In one of the patients, no AED changes were made. The alterations in AED regimen enacted during the follow-up are presented in Table 2. In the group of nonresponders to both therapies, one AED introduction was made between the neuromodulation therapies, causing the contradiction in total number of AEDs in the table. None of the responses to VNS or DBS are explained by the AED changes. The stimulation parameters were adjusted in every patient according to a similar protocol, with similar goal settings. We re-evaluated the stimulation setting histories and did not find any differences in the settings between the responders and nonresponders.

4 | DISCUSSION

According to our descriptive study, the response to ANT-DBS therapy seems to be clinically associated with the response to previous trial of VNS therapy; if a patient had a partial or progressive positive effect of VNS, the ANT-DBS effect also showed same feature. If the patient was not responding to VNS therapy at all, the chances for a stable DBS response were reduced. Interestingly, this study provides for a first time a long-term follow-up data for more than 10 years of patients with both VNS and DBS therapies. The follow-up data of the SANTE trial have been published recently (Salanova et al., 2015): The median seizure reduction with ANT-DBS compared with baseline for patients previously tried with VNS was 69% in five years, whereas the seizure reduction without prior VNS was also 69%. The reasons for VNS discontinuation were not reported. Therefore, their results differ from ours, as they did not report any similarities between the responses to VNS and ANT-DBS therapies.

This discrepancy between our results is most likely due to the different nature of the SANTE trial patient population and our study population. The patients in the SANTE trial with previous VNS therapy were classified as nonresponders; however, the reasons for VNS explantation may vary including scar formation with impedance problems, battery depletion, or dissatisfaction with obtained response, and the study might contain a group of patients with heterogeneous responses ranging from total nonresponders to partial responders. The patients for clinical trials are selected by more rigorous assessments than it is the case in everyday clinical practice. Most likely, in the SANTE trial, patients with a good response to VNS were not included. In our study population, some good VNS responders were indeed changed to DBS therapy, owing to the fact that at the time of the decision to proceed to DBS, the full effect of VNS was not acknowledged. Also, it has to be taken into consideration that our patients were not fully satisfied with the VNS response and wanted to have it better in spite of being responder to VNS according to conventional evaluation.

Our study demonstrates that the reasons for discontinuing VNS treatment can be variable. Some patients did not have any effect of VNS on seizure frequency, therefore forming one distinct group. Most

TABLE 2 Antiepileptic drug schedule alterations during the follow-up

Responder status to VNS & DBS therapies	Initiative AEDs (average count)	AED changes during VNS therapy	AED count on DBS implantation (average count)	AED changes during DBS therapy	AED count at the end of the follow-up (average count)
Progressive & progressive (n = 3)	3	2 introductions 3 decreases 1 discontinuation	3.33	1 introduction 1 decrease 1 discontinuation	3.33
Partial & partial (n = 2)	2	1 introduction 3 increases 1 discontinuation	2	1 introduction 2 increases 1 decrease	2.5
No & no (n = 5)	2.4	1 introduction 2 increases 2 decreases 2 discontinuations	2.2	3 introductions 2 increases 1 decrease 2 discontinuations	2.6
No & progressive (n = 1)	3	3 introductions 1 decrease 1 discontinuation	5	2 introductions 1 increase 3 discontinuations	4

of the patients with VNS treatment showed some response to the treatment. Furthermore, one patient group had an initial response fulfilling the traditional criteria for responder, but later lost this response despite continuous effective VNS treatment forming a group of fluctuating partial responders. This group cannot be considered as real responders, however, but form an interesting group of patients as they seem to respond to both VNS and ANT-DBS in a similar way, although the effect could also be explained by the fluctuating nature of the disease. A third group demonstrated a progressive decrease in seizure frequency until VNS therapy was either intentionally or unintentionally (battery depletion) terminated, or the therapy was no longer effective due to high impedance situation. There was a high impedance situation in three of 11 patients in our study group, which is quite exceptional and does not present the usual prevalence within our center. In high impedance situations, we tend to consider other treatment options along with the lead revision surgery. Another option for some of our patients could have been re-implantation of the VNS electrodes or simply battery replacement, instead of commencing the DBS therapy. In clinical setting, some VNS responders were considered as nonresponders, which was realized afterward in the retrospective analysis. There is also an option of re-introducing VNS therapy in combination with ANT-DBS therapy for a possibility of additive efficacy. These findings highlight the importance of precise and detailed information about seizures, for example, seizure diaries and careful patient follow-up, performed in our study in a single epilepsy center and by one epileptologist (JP). Furthermore, before altering the treatment method from VNS to DBS (or vice versa), a long-term follow-up of different seizure types and their frequency should be carefully assessed.

Along with the neurostimulation treatment, the patients were treated with antiepileptic drugs in accordance with standard clinical practice. Within the patients responding to VNS and DBS therapies, the AED regimen alterations do not seem to cause significant effects on seizure frequencies, even though the total AED amount being slightly increased during the follow-up period. None of the responders to VNS or DBS were so because of the AED changes.

There are data suggesting commonalities in VNS and ANT-DBS treatments. VNS increased cerebral blood flow (CBF) to the right thalamus among other structures such as the right posterior temporal cortex (Ko et al., 1996). Additionally, in PET studies blood flow was increased to the inferior cerebellum, hypothalamus, and thalamus and decreased in the areas of the hippocampus, amygdala, and posterior cingulate gyrus during VNS (Henry et al., 1998). In a subsequent study, increased right and left thalamic CBF correlated with decreased seizures suggesting that increased thalamic synaptic activities probably mediate some anticonvulsant effects of VNS (Henry et al., 1999). The main conclusions from these studies are that the thalamus is consistently involved in VNS therapy (Ben-Menachem, 2002), which lend support to the hypothesis that DBS stimulation of the ANT with prominent connections with limbic circuitry affects similar structures with VNS. One might speculate that the similar responses to VNS and DBS therapy in our patient population might be partly explained by this neurobiological concept.

On the one hand, the main limitation of our study is the small number of patients with both VNS and DBS treatments limiting the possibilities for statistical analysis. On the other hand, all previous ANT-DBS studies with the exception of the SANTE (Salanova et al., 2015) trial comprise similar numbers of patients. We also provide long-term follow-up data for more than seven years for each patient. Another significant weakness of our study is that the data are collected retrospectively and the trial is unblinded and nonrandomized, therefore increasing the risk of bias in the results. Moreover, some segment of the response might be fallacious due to the fluctuating nature of the disease.

As a conclusion, this is the first study to evaluate in detail the effect of both VNS and ANT-DBS therapies in refractory epilepsy patients. Our study provides some provisional data suggesting an interesting relationship between responses to two modalities of neurostimulation. The main feature of our study is to form a hypothesis for further analysis. Much information on the detailed VNS response in patients with subsequent ANT-DBS therapy is needed to assess the definitive significance of this putative association.

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CONFLICT OF INTEREST AND SOURCES OF FUNDING

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PUBLICATION II

Autostimulation in Vagus Nerve Stimulator Treatment: Modulating Neuromodulation

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Autostimulation in Vagus Nerve Stimulator Treatment: Modulating Neuromodulation

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Objectives: Until now, the vagus nerve stimulation (VNS) treatment in epilepsy has consisted of two different modes: normal and magnet stimulation. A new vagus nerve stimulator model (106 AspireSR®, LivaNova, Houston, TX, USA) also allows automatic stimulation (AutoStim). The purpose of this study is to examine the effect of autostimulation on seizure frequencies together with energy consumption.

Materials and Methods: The study material consisted of 14 patients whose former stimulator model (102/103) was replaced with model 106. We calculated the theoretical charge (Q) in Coulombs for one day in both of those groups. We evaluated the follow-up data of the patients' seizure counts, with a mean follow-up time of 18.1 months (SD 8.1).

Results: The total charge, "VNS dose," was reduced with model 106 in comparison with models 102 or 103 ($p = 0.001$, Mann–Whitney test). The average charge (Q_{total}) for one day with AutoStim was 142.56 mC; without AutoStim, it was 321.09 mC. We were able to assess seizure diaries in 11 out of 14 patients. Four patients (36%) had >50% seizure reduction and two patients (18%) experienced a reduction in seizure severity with VNS with autostimulation. Five patients (46%) remained unchanged. In three out of four patients with improved seizure control, the duty cycle was maintained at the original level. The patients whose duty cycle was modified for a more prolonged OFF-time had unchanged seizure frequencies.

Conclusion: VNS with AutoStim achieves maintenance of prior-established seizure control with markedly less energy consumption and can also improve seizure control as compared to former stimulator model.

Keywords: Autostimulation, epilepsy, neuromodulation, seizure, vagus nerve stimulation

Conflict of Interest: Joonas Haapasalo has received support for travel to congresses from Medtronic and Stryker. Kai Lehtimäki has received consultation fees and speaker honoraria from Medtronic and Abbott (former St. Jude Medical). Sirpa Rainesalo has received speaker honoraria from Fenno Medical, Orion Pharma, and UCB. Jukka Peltola has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for LivaNova, Eisai, Medtronic, UCB, and Pfizer. The remaining authors have no conflicts of interest.

INTRODUCTION

Until recently, the vagus nerve stimulation (VNS) treatment in epilepsy consisted of two different modes, normal mode and magnet mode stimulation. VNS is proposed to have three different mechanisms of action: 1) immediate termination of a seizure (1), 2) short-term anticonvulsive effect of stimulation (2), and 3) long-term effects on neural circuitries (3). Normal mode cyclic stimulation exerts major effects via the two latter mechanisms whereas the magnet mode is thought to interrupt the seizures. A newly introduced model (106 AspireSR®) exploits a novel treatment mode based on heart rate variability, i.e., autostimulation (also known as closed-loop VNS).

It may be challenging to apply the magnet mode stimulation due to several reasons. Therefore, a biomarker reflecting initiation or ongoing seizure activity was needed in order to automatically activate the VNS device. Ictal tachycardia is a well-known manifestation of epileptic seizures, especially in temporal lobe seizures—tachycardia seems to be present at seizure onset in 82% of patients, and on average in 64% of all generalized and in 71% all focal onset seizures (4). Moreover, focal to bilateral tonic–clonic seizures often lead to greater and longer lasting tachycardia than encountered with focal seizures (5). Furthermore, even though being rare, ictal bradycardia is also a possible manifestation of a seizure (6), although there is some evidence to suggest that patients with ictal bradycardia benefit less from VNS therapy (7).

An algorithm based on ictal heart rate variation is included in the VNS model 106 which initiates an automatically triggered stimulation to terminate an ongoing or imminent seizure. The proof of concept was demonstrated in a videoEEG study that revealed that autostimulation was triggered by the epileptic

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seizure in a substantial part of the seizures and furthermore, it was able to terminate some seizures (8).

At present, there is a lack of data concerning the long-term effect of VNS with AutoStim features. In one study with 20 VNS patients with a one-year follow-up, AutoStim and the extra stimulations did not significantly affect power usage, since the measured duty cycles increased from a baseline of 11% with stimulation to about 16% when Normal Mode, AutoStim, and Magned Mode were combined, all on at six months (9). The majority, 74%, of focal impaired awareness seizures (FIAS) and focal to bilateral tonic clonic seizures (FBTCS) evoked at least a 20% increase in the heart rate. A total of 31 out of 89 seizures (35%) triggered AutoStim and 19 (61%) were terminated by AutoStim. Another study detailed the median parameters used at the 6- and 12-month follow-ups (10). In this study, 10/66 (15%) of all seizures were detected and terminated with AutoStim. These two studies did not have a comparison group without AutoStim properties. As a summary, one-fifth of the seizures were detected and terminated by the automatic stimulation. According to these results, it seems that automatic stimulation functions as intended and is well-tolerated.

There are several open questions regarding the clinical use of automatic stimulation in VNS. What are the optimal parameters for its use? How should the normal mode and AutoStim mode settings be programed after the initiation of AutoStim? What is the amount of AutoStims with different threshold rates? How does the AutoStim affect the power usage? The purpose of this study is to elucidate these features of automatic stimulation mode of VNS therapy in a retrospective group of patients with refractory epilepsy. As far as we are aware, this is the first study to evaluate the novel possibilities accessible with the 106 AspireSR in comparison to the older VNS models.

MATERIALS AND METHODS

Since the study was a noninvasive and retrospective study, it does not oblige ethics committee approval according to Finnish Law on Research. The study material consisted of VNS treated patients with refractory focal epilepsy who had previously been using the traditional VNS treatment modalities (normal and magnet mode), and after their generator was replaced by the new 106 AspireSR®, they had the autostimulation mode activated. There were 12 patients with the VNS model 102 implanted which were subsequently replaced with model 106. In addition, there were two patients who had model 103 and who were upgraded to model 106. The follow-up time varied from 7 to 32 months (mean 18.1 and SD 8.1) with the model 106. The duty cycle was altered in 10 out of 14 patients by prolonging the OFF-time. We decreased output current in six and frequency in two patients based on clinical decision to adjust these parameters to the standards in accordance of our own hospital guidelines (Table 2).

The total amount of stimulation was listed as follows 1) as the percentage of ON-time on a daily basis (separately normal mode, autostimulation mode, and magnet mode), also known as the therapy time, and 2) as the total amount of charge (in Coulombs) delivered in 24 hours comparing situations with or without autostimulation. In addition, the total number of automatic activations and normal mode and magnet mode stimulations were counted as daily averages along with the accurate data of all changes made in the VNS settings. Statistical analyses were performed using SPSS 20.0 software.

Seizure control with regard to stimulation parameters was assessed. The baseline in the seizure frequencies was evaluated as the average monthly count of seizures for 12 months with the older VNS model. Five of the patients had been followed up in other Finnish hospital prior to their referral for re-implantation in our center, and the battery had become depleted in four of them, i.e., this represented a separate OFF-period before they received the new VNS model. After re-implantation, they were followed up in Tampere University Hospital. With respect to model 106, the seizure counts were monthly averages during consecutive periods of six months. A patient was considered as a responder, if for the majority of the VNS model 106 follow-up period, the seizure reduction was at least 50% or there was a progressive improvement in seizure count achieving at least a 50% decrease in seizure frequency in terms of disabling seizures, e.g., seizures interrupting activities of daily living. Fifty percent of seizure reduction was compared to pre-Aspire frequency. Along with the total number of seizures, we also analyzed the severity of the seizures. Seizures were classified according to the new ILAE classification for seizures (11). Seizure frequencies were assessed using individualized seizure diaries and the seizure count, type, and severity were estimated. The seizure diaries for three patients were not assessable.

The patients' AED medication and the changes of medication are presented in Table 1. Nine out of the total 14 patients (64%) did not experience any changes in their AED regimen whereas in the remaining five patients (36%), some changes were undertaken, mostly reductions in drug therapy. Furthermore, in two patients, new drugs were initiated during the follow-up without any effect on seizures. In one patient (#7), perampanel was initiated and later discontinued due to side-effects and in one patient (#13), brivaracetam was initiated and later stopped due to a lack of efficacy, that trial being the only change in AED therapy in this patient.

In the statistical analysis, the latest (assumed to be the most efficient) normal mode stimulation settings and the latest settings with AutoStim were used. We calculated the theoretical charge (Q) in Coulombs for one day in both of those groups, as follows (12).

$$Q_{\text{total}} = \left(\frac{T_{\text{period}} \left(\frac{I}{1000}\right) \left(\frac{\text{Pw}}{10^6}\right) f (t_{\text{ON}} + 4)}{t_{\text{ON}} + (t_{\text{OFF}} * 60)} \right)$$

Q_{total} = total charge (C), T_{period} = time period (sec), I = output current (mA), Pw = pulse width (msec), f = pulse frequency (Hz), t_{ON} = ON-time (sec), t_{OFF} = OFF-time (min). T_{period} is 86,400 sec in this analysis, equals one day.

In order to use the formula with AutoStim patients, we calculated the t_{OFF} value as follows (13). Four seconds added to ON-time represents the ramp time at the start and end of each stimulation

$$t_{\text{OFF}} = \frac{t_{\text{ON}} + 4}{\text{ON}\%} - t_{\text{ON}}$$

t_{OFF} = OFF-time (sec), t_{ON} = ON-time (sec), ON% = duty cycle (%/100).

RESULTS

With the exception of patient #5, in all of the other patients, the total charge delivered in one day was reduced, as described in detail in Table 2. The mean decrease in Q was 178.5 mC

Table 1. Patient Characteristics.

Id	Sex	Age*	Medication → at the last visit	MRI	Etiology	Seizure onset zone	Seizure type	Responder to VNS 106
1	F	62	ZNS 500 mg LTG 400 mg	Focal parietal lobe cortical dysplasia on the left side	CD	Parietal lobe	FAS FAM FIAM	Yes
2†	F	50	CBZ 1000 mg PGB 600 mg	Normal	Unknown	Frontotemporal	FAba FIAa	Yes
3†	F	35	PGB 600 mg → 0 LCM 600 mg PER 6 mg CLB 30 mg → 15 mg	Perisylvian polymicrogyria on the left side	CD	Temporoparietal	FASa FIAa	No
4†‡	F	26	OXC 1800 mg LEV 3000 mg TPR 300 mg	Normal, left hippocampus smaller	Unknown	Bilateral temporal lobe	FIAa	No
5‡	F	16	VPA 900 mg → 500 mg LTG 200 mg LCM 150 mg → 200 mg	Bilateral lissencephaly on occipital lobes	CD	Bilateral occipital lobe	FIAM FIAba	Yes
6	M	26	VPA 1200 mg LTG 200 mg	Widespread confluent calcifications, centrocortical atrophy	Labrune's disease	Temporal lobe	FIAa PNES FBTCS	No
7	M	30	OXC 600 mg LCM 500 mg RTG 900 mg → 0 mg	Postoperative diffuse glial changes, secondary brain traumas	Postradiation	Frontal lobe	FIAM short and long	Not assessable
8	F	38	CBZ 600 mg → 0 mg LEV 2000 mg ZNS 400 mg	Widespread bilateral symmetric band-heterotopia	CD	Multifocal	FIAba FANMc	Yes
9	F	38	LCM 600 mg ZNS 400 mg LEV 3000 mg	Normal	Meningoencephalitis	Multifocal	FIANM/S FIAM FIAba	Not assessable
10	F	37	LTG 500 mg ZNS 300 mg	Widespread cortical dysplasia, bilateral frontoparietal band-heterotopia	CD	Multifocal	FBTCS	No
11	M	29	LCM 400 mg LEV 1000 mg TPR 350 mg CLB 10 mg OXC 1200 mg	Normal	Unknown	Frontal lobe	FIAhk	Not assessable
12	F	34	CLB 10 mg LTG 500 mg ZNS 400 mg	Widespread vascular changes	Perinatal vascular lesion	Multifocal	FIANM FIAM	Decrease in seizure severity
13	M	50	OXC 1800 mg	Normal	Unknown	Temporal lobe	FANMc	No
14†	M	37	CBZ 800 mg LTG 400 mg LCM 400 mg CLB 20 mg	Normal	Unknown	Temporo-occipital	FIAM	Decrease in seizure severity

Medication: AED regimen at the beginning of follow-up. After the arrow, the changes in AEDs are presented. BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PER, perampanel; PGB, pregabalin; RTG, retigabine; TPR, topiramate; VPA, valproate; ZNS, zonisamide.

Seizure types: FAba, focal aware with behavioral arrest; FAM, focal aware motor; FANMc, focal aware nonmotor cognitive; FAS, focal aware sensory; FASa, focal aware seizure with autonomic symptoms; FBTCS, focal to bilateral tonic clonic; FIAa, Focal impaired awareness with automatisms; FIAba, focal impaired awareness with behavioral arrest; FIAhk, focal impaired awareness hyperkinetic; FIAM, focal impaired awareness motor; FIANM, focal impaired awareness nonmotor; FIAS, focal impaired awareness sensory; FNMc, focal nonmotor cognitive; PNES, psychogenic nonepileptic seizure.

*Age when VNS model 106 was implanted.

†Battery depletion before implantation of VNS model 106.

‡Model 103 before 106 was provided.

Table 2. Settings and Amount of Stimulations of VNS.

Id	Initiative settings	Settings changed	Change in total *Q*	Mean number of total daily stimulations	Mean number of daily AutoStims	Therapy time (%)	Share of AutoStims (%)	Lead Impedance (Ω)
1	*I*: 1.25 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	t_{OFF}: 0.8 min → 1.1 min HB sens. Setting: 5 Threshold: 20%	Δ*Q* = 235.4 mC → 194.4 mC = 41 mC = 17.4% reduction	943	166	36	17.6	2559
2	*I*: 2.25 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 1.1 min	*I*: 2.25 mA → 1.5 mA HB sens. Setting: 2 Threshold: 20%	Δ*Q* = 344.3 mC → 168.5 mC = 175.8 mC = 51% reduction	705	178	26	25.2	2674
3	*I*: 2.25 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	*I*: 2.25 mA → 1.75 mA *f*: 20 Hz → 30 Hz t_{OFF}: 0.8 min → 3 min HB sens. Setting: 2 Threshold: 20%	Δ*Q* = 423.7 mC → 226.8 mC = 196.9 mC = 46.5% reduction	533	320	20	39.8	27
4*	*I*: 2.75 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 3 min	*I*: 2.75 mA → 1.75 mA t_{OFF}: 3 min → 5 min HB sens. Setting: 2 Threshold: 30%	Δ*Q* = 192.3 mC → 121.0 mC = 71.3 mC = 37.1% reduction	445	285	16	64.0	2507
5*	*I*: 1.75 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 3 min	HB sens. Setting: 4 Threshold: 40%	Δ*Q* =122.4 mC → 128.5 mC = 6.1 mC = 4.7% increase	439	53	17	12.1	2540
6	*I*: 1.75 mA Pw: 250 µsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	*f*: 30 Hz → 20 Hz t_{OFF}: 0.8 min → 5 min HB sens. Setting: 1 Threshold: 40%	Δ*Q* = 494.3 mC → 75.6 mC = 418.7 mC = 84.7% reduction	288	49	10	17.0	2183
7	*I*: 2.5 mA Pw: 250 µsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	*I*: 2.5 mA → 1.75 mA t_{OFF}: 0.8 min → 1.8 min HB sens. Setting: 1 Threshold: 20%	Δ*Q* = 706.2 mC → 283.5 mC = 422.7 mC = 59.9% reduction	666	102	25	15.3	2854
8	*I*: 1.25 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 3 min	HB sens. Setting: 3 Threshold: 40%	Δ*Q* = 87.4 mC → 86.4 mC = 1 mC = 1.1% reduction	429	40	16	9.3	1845
9	*I*: 1.5 mA Pw: 250 µsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	*f*: 30 Hz → 20 Hz t_{OFF}: 0.8 min → 5 min HB sens. Setting: 3 Threshold: 30%	Δ*Q* = 423.7 mC → 64.8 mC = 358.9 mC = 84.7% reduction	290	41	10	14.14	2513
10	*I*: 3 mA Pw: 250 µsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 5 min	*I*: 3 mA → 1.75 mA HB sens. Setting: 3 Threshold: 30%	Δ*Q* = 200.3 mC → 147.4 mC = 52.9 mC = 26.4% reduction	365	172	13	47.1	2228
11	*I*: 1.5 mA Pw: 250 µsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 1.1 min	*I*: 1.5 mA → 1.75 mA t_{OFF}: 1.1 min → 5 min HB sens. Setting: 1 Threshold: 20%	Δ*Q* = 344.3 mC → 147.4 mC = 196.9 mC = 57.2% reduction	364	164	13	45.1	2771
12	*I*: 1.5 mA Pw: 250 µsec *f*: 20 Hz t_{ON}: 30 sec t_{OFF}: 0.8 min	t_{OFF}: 0.8 min → 5 min HB sens. Setting: 3 Threshold: 20%	Δ*Q* = 282.5 mC → 90.7 mC = 191.8 mC = 67.9% reduction	377	192	14	50.9	2912

Table 2. *Continued*

Id	Initiative settings	Settings changed	Change in total *Q*	Mean number of total daily stimulations	Mean number of daily AutoStims	Therapy time (%)	Share of AutoStims (%)	Lead Impedance (Ω)
13	*I*: 1.5 mA Pw: 250 μsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 1.8 min	t_{OFF}: 1.8 min → 5 min HB sens. Setting: 3 Threshold: 20%	ΔQ = 239.5 mC → 136.1 mC = 103.4 mC = 43.2% reduction	402	225	14	56.0	2898
14	*I*: 2.5 mA Pw: 250 μsec *f*: 30 Hz t_{ON}: 30 sec t_{OFF}: 1.8 min	*I*: 2.5 mA → 1.75 mA t_{OFF}: 1.8 min → 5 min HB sens. Setting: 3 Threshold: 40%	ΔQ = 399.1 mC → 124.7 mC = 274.4 mC = 68.8% reduction	329	122	11	37.1	1959

I, output current (mA); Pw, pulse width (μsec); *f*, pulse frequency (Hertz); t_{ON}, ON-time (sec); t_{OFF}, OFF-time (min).
*Model 103 before 106.

(ranging from −6.1 to 422.7 mC, mean 178.5, and SD 140.7; Fig. 1). This effect is explained by the altered normal mode stimulation settings. In addition, according to our own VNS programming protocol, the target current is usually 1.75 mA, whereas some patients referred from other hospitals had had higher therapeutic currents.

When the normal mode stimulation settings were not altered (patients #5 and #8), the value of *Q* was also not altered; +6.1 and −1 mC, correspondingly. However, in those patients, the threshold rate for autostimulation was relatively high, 40%, and therefore also the percentage shares of automatic stimulations were low, 12 and 9% (Table 2).

The change in the charge delivered by the different VNS models is presented in Figure 1. The total charge delivered in an individual patient in one day was significantly less when utilizing the AutoStim properties; this result was statistically significant (p = 0.001, Mann–Whitney test). In the statistical analysis, we used the total *Q* values with the final settings with the older models, and the final settings with model 106. Therefore we have two different *Q* values for all of the 14 patients for comparative analysis.

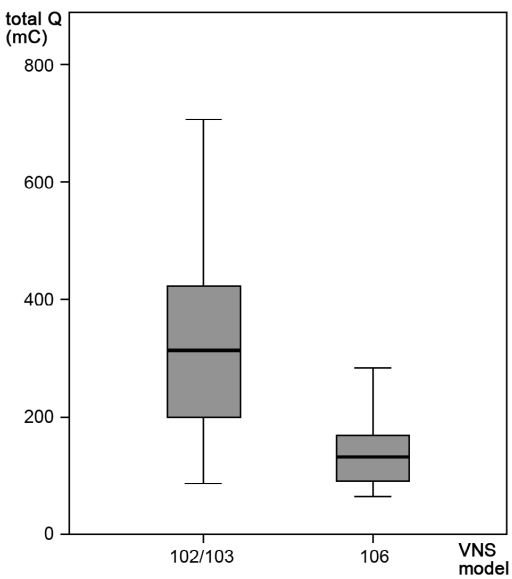

Figure 1. The total charge delivered in one day in Coulombs with different VNS models. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 2 shows the stimulation specifics and seizure information of the patients responding to the VNS model 106 therapy. The first time point represents the baseline, i.e., 12 months of follow-up with an older VNS model. The OFF-phase is the time when the patients' batteries were depleted, i.e., before implanting the new model. With the new model, the time-points represent consecutive six-month periods. The seizure counts are monthly averages during the six-month periods. The AutoStim properties are the device settings and information gathered from the last outpatient visit during every six-month time period. The information retrieved from the stimulator (therapy time, share of AutoStims, and total *Q*) applies to the time before the outpatient clinic visit, with the VNS settings presented. The therapy time (%) with the older model of VNS was calculated by dividing the ON-time +4 sec by the duration of the whole stimulation cycle (t_{ON} + 4 sec)/(t_{ON} + t_{OFF})). An additional 4 sec were added to the ON-time in order to account for ramping periods during the initiation and termination of stimulation bursts (12).

We were able to assess the changes in seizure frequencies in 11 out of 14 patients. Four of them (36.4%) were responders to the VNS therapy with AutoStim properties, enjoying at least a 50% reduction in seizure frequency. Five (45.5%) did not experience any significant change in seizure frequencies. Two patients stated that the severity of their seizures had declined, therefore they were considered as "qualitative responders," even though the number of seizures was not reduced significantly. One of the nonresponders reported experiencing less intense breathing problems and none of the patients suffered more seizures with AutoStim than without it.

Only one out of four of the patients with battery depletion before the re-implantation, had been keeping a quantitative seizure diary, but all of the patients reported that they suffered an increase in seizure frequency or severity when the VNS was OFF.

For patients #12 and #14, the responder status was defined as "decrease in seizure severity." After the initiation of VNS model 106, the awareness of patient #12, was notably less impaired during the seizures, than before. We were not able to assess the

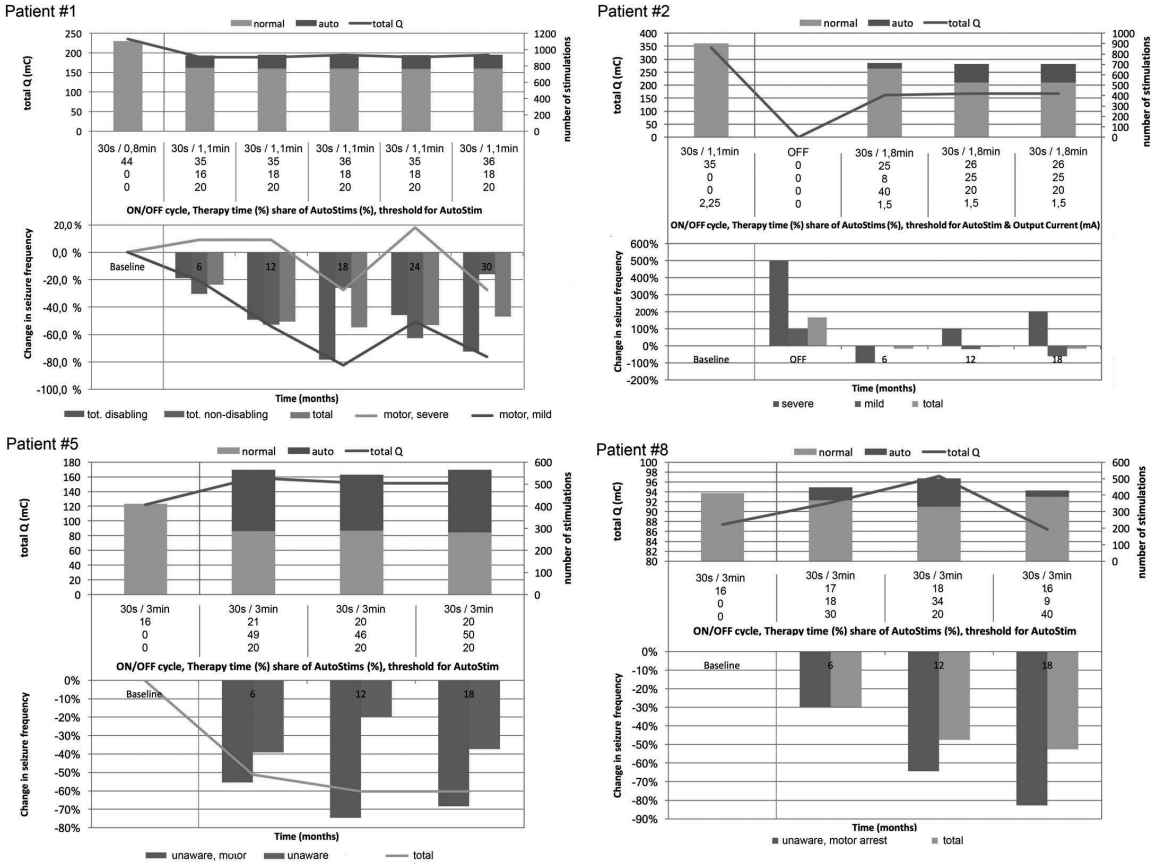

Figure 2. Distribution of electric charge delivered in those patients responding to VNS AspireSR® therapy compared to the baseline. The implantation of model 106 is designated with a vertical line. If the Output Current is not presented, it remained unaltered. In the lower part of the figure, the alterations in seizure frequencies are presented with regard to different seizure types. [Color figure can be viewed at wileyonlinelibrary.com]

exact seizure frequencies in patient #14 due to the lack of follow-up information about the seizures occurring during the VNS treatment with model 102. After the initiation of VNS, this patient did not experience any daytime seizures and those seizures that did occur had a shorter duration.

DISCUSSION

Two main findings emerge from this study; first, the initiation of automatic stimulation in VNS therapy seemed to display positive efficacy with respect to seizure frequency, therefore also leading to the possibility of reducing the AED burden. Second, the power usage with the new VNS model was significantly less than with the older models.

According to our results, the autostimulation may offer a possibility for better seizure control, but final conclusions cannot be made without double blinded prospective trials. Four out of 14 patients were designated as responders with at least a 50% decrease in seizure frequency when comparing to baseline before changing from a standard (Model 105 or earlier) to the AspireSR® device; in addition, two other patients experienced a reduction in seizure severity. In general, the response to VNS seemed to be progressive, with seizure frequencies decreasing over time during long treatment periods, as also reported by others (14). As seen in our responders, the effect intensified over time (Fig. 2). Since patients receiving VNS therapy are usually also treated with drugs, it can be difficult to determine if the beneficial effects are attributable to the medication or VNS. It has been questioned whether VNS had any effect on seizures since the AED regimen changes were also initiated during VNS therapy and these may have exerted an important effect on seizures (15). In our study, two out of four responders (50%) had their AED burden reduced after implantation of model 106 and initial decrease in seizure frequency which was sustained even after AED reduction. Nonetheless, in two patients who experienced a decrease in seizure severity, no AED changes were made. Thus, all of the responders were responding because of the new VNS device with autostimulation property. The improvement during autostimulation therapy was much more profound than the usual continued improvement over time with neurostimulation. The degree of improvement seen with switch to an AspireSR® device was numerically greater than the improvement over time seen with continued use of the Model 105 (14). However, our study is not designed or powered

to document a statistically significant difference, which will await future studies.

According to our results, the implantation of the new VNS model with its autostimulation capabilities, significantly reduced the total current usage, as described by total *Q*. Our results are strongly associated with the other configurations of the device, as seen in Table 2. Due to the autostimulation and better seizure control, it is possible to prolong the OFF-time, which leads to significantly reduced power usage. The initiation of AutoStim itself does not seem to increase power usage prominently (9). The normal mode stimulation cycle was prolonged in ten patients, only one of them being a responder; in three out of four (75%) responders, the duty cycle remained unaltered. The duty cycle seemed to be shorter in the responders (mean t_{OFF} 90 sec) in comparison with the nonresponders (mean t_{OFF} 269 sec). Two out of four responders did not display any notable changes in power usage. In the responders, the mean reduction in total *Q* was 16.2%, whereas in the nonresponders, it was 57.6%. In our center, we previously have had to treat patients from different hospitals; in these patients, there is no accurate information about the protocol used to configure the device. Furthermore, in some patients, e.g., #10, the output current was unnecessarily high, leading to faster battery depletion. There is now an awareness that these kinds of high currents are unnecessary since almost all of the fibers in the vagus nerve can be activated already with a current of 1.5 mA (16), even though the scar tissue forming around the nerve ultimately might insulate the nerve, requiring the output current to be elevated. Today, according to our protocol, the target output current for the patients is 1.75 mA. If one encounters efficacy problems with that output current, then the next step is to alter the duty cycle or autostimulation properties.

Autostimulation is delivered daily, perhaps even more than 300 times, depending on the stimulation threshold. Therefore, it may also exert a possible effect on two other mechanisms of action, i.e., short-term anticonvulsive and long-term neuromodulatory changes. In closed-loop responsive deep brain stimulation, the train of stimulation is triggered by EEG activity associated with seizure related changes, i.e., in a similar manner as exploited in VNS autostimulation. In a DBS closed-loop stimulation, the system is activated up to 2000 times daily, therefore emphasizing the long-term neuromodulatory role of this form of treatment, in addition to acute seizure termination. VNS autostimulation changes the profile of the daily stimulation from constant stable cycling (e.g., 30 sec ON/3 min OFF) to a more variable delivery based on heart rate variation induced activation on the top of constant cycling, which also have been postulated to confer a possible beneficial effect on seizure control. The effects of introducing automatic stimulation with a low autostimulation activation threshold and with unaltered normal mode stimulation settings, still need to be clarified in future studies.

The use of autostimulation has wider repercussions than simply terminating the ongoing seizure. One pivotal video EEG study demonstrated also the importance of sensitivity and specificity issues (10). The 106 AspireSR® model can be programmed to respond to different increases in the heart rate algorithm, ranging from 20 to 70%. The lower the threshold, the more seizures that would be detected. This data implies that it is optimal to use the lowest detection threshold in order to maximize the possibilities of seizure detection. This emphasis on sensitivity naturally leads to reduced specificity. The issue of specificity has raised concerns of increased use of power, leading to faster battery depletion and problems with tolerability; for instance, those associated with athletic performances. The automatic stimulations during physical (at least 3 min of stair stepping) exercise have also been assessed (10). In 55.9% of 127 exercises, the AutoStim did not become triggered at all, in 20.5% of the sessions AutoStim was triggered once and in the remaining 23.6% of sessions, AutoStim was triggered twice.

In addition to detecting ictal tachycardia, there are some other ways to predict an imminent seizure. Some patients experience prodromal symptoms and there may be evidence of altered brain activity before the seizures. Functional MRI and near-infrared spectroscopy have detected elevated perfusion before the seizures. Transcranial magnetic stimulation experiments have revealed that the brain is in a hyperexcitable state prior to a seizure. There is also a seizure advisory system that analyzes EEG in real-time by recording the brain activity intracranially, then emitting a signal of an imminent seizure to help patients to seek treatment even before the clinical seizure has started (17). There are also non-EEG based wrist-worn seizure detecting systems under development, with promising results (18). According to one hypothesis, the interictal spikes in EEG are a consequence of increased neural excitability, possibly leading to a seizure. Other hypotheses suggest that spikes might also have a beneficial effect with regard to the seizures as the spikes are often followed by period of hyperpolarization, which may limit the interictal activity and regulate the propagation of the seizure. In one study with 15 participants, nine of the patients experienced a significant change in the spike rate prior to the seizures. In six of them, the spike rate had declined (19).

The main limitation of this study is the small number of the patients. Since it is a retrospective study, the follow-up before initiating the VNS therapy with the new model, was not truly systematic and in some patients, the seizure diaries were not accessible.

This study provides preliminary information and promising results regarding the efficacy of the automatic stimulation properties of a vagus nerve stimulating device. All of the 14 patients have received VNS treatment for years and experienced a sustained efficacy with older models of VNS, i.e., every patient was already a responder to VNS therapy. According to the Tampere protocol for VNS treatment, these patients would have proceeded to other treatment options if they had not displayed a response to the VNS treatment with the first implantation. After battery depletion, these 14 patients were provided with the new model of VNS and three (21%) of them showed at least a 50% improved response in seizure frequency when compared to the older model of VNS, and additionally one patient achieved at least a 50% seizure reduction compared to the time when VNS was OFF between the VNS therapies. In addition, the total charge used by the stimulator, was significantly reduced with the new model. Theoretically, the reduced power usage should lead to longer battery life. In the future, the follow-up of the patients will reveal how the autostimulation modality affects the battery life.

CONCLUSIONS

In patients known to respond to VNS therapy with a normal mode stimulation, the initiation of automatic stimulation mode has the potential to prolong the duty cycle with reduced power usage and possibly also to prolong the battery life. The same seizure control was achieved with the same or reduced total charge delivered to the patient. According to our results, some patients

may also experience improvements in their seizure control over a time period of 12–18 months when autostimulation is activated, with the same or slightly longer OFF-times in comparison with previous VNS models.

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Authorship Statements

Drs. Kulju, Peltola and Haapasalo designed the study and conducted the data analysis. Drs. Kulju and Peltola gathered the data. All authors approved the final manuscript. All authors participated in the writing of this study. Dr. Kulju prepared the manuscript draft.

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PUBLICATION III

Frequency of Automatic Stimulations in Responsive Vagal Nerve Stimulation in Patients With Refractory Epilepsy

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Frequency of Automatic Stimulations in Responsive Vagal Nerve Stimulation in Patients With Refractory Epilepsy

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ABSTRACT

Background: In vagal nerve stimulation (VNS) therapy, the release of VNS model 106 (AspireSR) allowed for responsive VNS (rVNS). rVNS utilizes a cardiac-based seizure detection algorithm to detect seizure-induced tachycardia to trigger additional stimulation. There are some studies suggesting clinical benefits of rVNS over traditional VNS, but the performance and significance of autostimulation mode in clinical practice are poorly understood.

Objectives: To assess the effect of initiation of rVNS therapy and altered stimulation settings on the number of daily stimulations and energy consumption in VNS therapy and to compare autostimulation performance in different epilepsy types.

Materials and Methods: Retrospective follow-up of 30 patients with drug-resistant epilepsy treated with rVNS including 17 new implantations and 13 battery replaces at a single center in Finland. Our data consist of 208 different stimulation periods, that is, episodes with defined stimulation settings and both autostimulation and total stimulation performance-related data along with clinical follow-up.

Results: The variation in autostimulation frequency was highly dependent on the duration of the OFF-time and autostimulation threshold ($p < 0.05$). There was a large additional effect of autostimulation mode on therapy time and energy consumption with longer OFF-times, but a minor effect with shorter OFF-times. Significantly more autostimulations were triggered in the temporal lobe and multifocal epilepsies than in extratemporal lobe epilepsies.

Conclusions: The initiation of autostimulation mode in VNS therapy increased the total number of stimulations. Shortening the OFF-time leads to a decreased number and share of automatic activations. Epilepsy type may affect autostimulation activity.

Keywords: Autostimulation, epilepsy, neuromodulation, seizure, vagus nerve stimulation

Conflict of Interest: Toni Kulju has received grants from Maire Taponen Foundation, Finnish Epilepsy Research Foundation, and City of Tampere Grant Committee. Joonas Haapasalo has received support for travel to congresses from Medtronic and Stryker. Ryan Verner is an employee of LivaNova PLC and holds stock options. Maxine Dibué-Adjei is an employee of LivaNova PLC and holds stock options. Kai Lehtimäki has received consultation fees and speaker honoraria from Medtronic and Abbott (former St. Jude Medical). Sirpa Rainesalo has received speaker honoraria from Fenno Medical, Orion Pharma, and UCB. Jukka Peltola has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for LivaNova, Eisai, Medtronic, UCB, and Pfizer.

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INTRODUCTION

One-third of epilepsy patients are considered to have drug-resistant (refractory) epilepsy (DRE), that is, sustained seizure freedom is not achieved with two tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (1-2). Resective epilepsy surgery is the first choice of care for DRE patients but is not feasible for everyone, for example, in a recent German study, less than 50% of patients underwent epilepsy surgery after presurgical evaluation on 2010–2013 (3). Neuromodulation therapies offer an alternative treatment option for this group of patients including vagal nerve stimulation (VNS), deep brain stimulation (DBS), and intracranial responsive neurostimulation (RNS). VNS has been available for more than 25 years with proven efficacy; at least 50% of the patients experience a 50–60% reduction in seizure frequency (4), and long-term outcomes (efficacy and safety) tend to improve with time (5-6).

The traditional cyclic (normal mode) VNS therapy consists of repetitive stimulations along with on-demand magnet mode stimulations when the patient or caretaker manually triggers the device for additional stimulation, often in response to an aura or active seizure. The stimulation patterns are produced in a pulse generator implanted into the upper chest and conducted to the left vagus nerve.

VNS model 106 (AspireSR) introduced a new mode of stimulation, autostimulation. Responsive VNS (rVNS) uses a cardiac-based seizure detection algorithm (CBSDA) to detect ictal tachycardia and trigger additional stimulations. A single-lead ECG (electrocardiograph) is recorded between the pulse generator and the cervical VNS electrode. The surgical implantation procedure is the same as for older systems (7). Similarly to normal mode and magnet mode stimulation settings, rVNS settings are individually programmable. The threshold for triggering autostimulation can be programmed from 20% to 70% increase in heart rate.

The ability of rVNS to detect and respond clinically to epileptic seizures has been suggested in preliminary studies (8-10), and patients with ictal tachycardia are proposed to be better responders for rVNS (11). Moreover, the improved efficacy after initiation of VNS with rVNS therapy has been emphasized in subsequent studies in both adults and children (12–14).

At present, a comprehensive understanding of the efficacy and function of rVNS therapy is lacking. We recently published a study assessing a group of 14 patients receiving rVNS therapy, with prior traditional VNS (models 102 and 103) therapy; in which we described the initiation of rVNS leading to better control of seizures and a decrease in AED burden (15). On the other hand, there is little data about the effect of different VNS settings on the number of stimulations and energy consumption, and there are no practical guidelines for the programming of the rVNS device.

As a sequel to our previous replacement study, we provide more data of rVNS performance, in both newly implanted rVNS patients and patients with prior VNS. All the patients received rVNS therapy in addition to the normal cyclic mode stimulation for the entire follow-up time. The aim of the present study was to assess the effect of different stimulation settings and the initiation of rVNS on the total number of daily stimulations and energy consumption. We also investigated whether there are differences in the function of rVNS in different epilepsy types.

MATERIALS AND METHODS

Patients

According to our local treatment guidelines, the majority of adult patients with refractory epilepsy (except some patients with moderate or severe intellectual disabilities) in Pirkanmaa Hospital District are treated at our institution, Tampere University Hospital. According to the Finnish Law on Research, approval of the Ethics Committee was not mandatory due to the nature of this study. In our patient selection for rVNS therapy, we do not evaluate the occurrence of ictal tachycardia.

Etiology was evaluated based on magnetic resonance imaging (MRI)-findings and clinical history. The classification of seizure types (16) and seizure onset zones were based on video-electroencephalograph (EEG) recordings and seizure characteristics. All the patients were treated with antiepileptic drugs (AEDs) in addition to rVNS therapy, mostly under a polypharmaceutical approach.

All patients who were implanted with an rVNS device during a time period between October 2014 and January 2017 in our institution, were included in the study. Our study group was 30 patients of which 13 received traditional VNS therapy before implanting the VNS model 106 AspireSR (LivaNova, Houston, TX, USA) allowing for automatic stimulation. All these patients were presented in our previous paper (15). One patient from the previous study was excluded because the follow-up was transferred to another hospital. Additionally, 17 newly implanted rVNS patients were recruited. Our VNS programming protocol scheme is presented in Figure 1.

Stimulation Data

The follow-up time for the present study started when automatic stimulation mode was initiated, on average 53 days after implantation, and autostimulation data were collected until the end of October 2017. All patients received VNS with rVNS therapy for the whole follow-up time. The patients visited the outpatient clinic between 1 and 12 times. In addition to routine data extraction, the rVNS device was checked for possible malfunctions.

In our programming protocol (Fig. 1) we opted to maximize the sensitivity of autostimulation trigger detection, thus minimizing the time delay to respond to seizures, for example, aiming for low threshold rates. This treatment strategy was selected based on the findings in the pivotal rVNS trial (9). Decreased specificity was not hypothesized to cause significant problems aside from tolerability-related issues that patients are able to report easily. Therefore, in most patients, the autostimulation was initiated with a 40% threshold, that is, 40% increase in the heart rate, to avoid unnecessary side effects in the beginning, when normal mode output current was still being increased. Autostimulation threshold was later decreased to 30% and further to 20% during subsequent clinical visits providing most of the stimulation periods with a 20% threshold. If tolerability issues arose, the threshold was increased. Normal mode duty cycles were shortened if clinical response was not satisfactory with an initial five-minutes OFF-time.

The total dataset for 30 patients consisted of 208 different sets of stimulation-related data (conceptualized as stimulation periods [SP] for the purpose of this study) containing the parameters for Output Current (mA), pulse width (usec), frequency (Hz), signal ON-time (sec), signal OFF-time (min), and the threshold for AutoStim (%). Therapy delivery information was also extracted: the number of stimulations in different categories (normal mode and AutoStim mode) as a daily average in a given stimulation period, and therapy time as a percentage of total ON-time. Magnet mode activation was allowed, although the data were excluded from the analysis due to the negligible amount of stimulations.

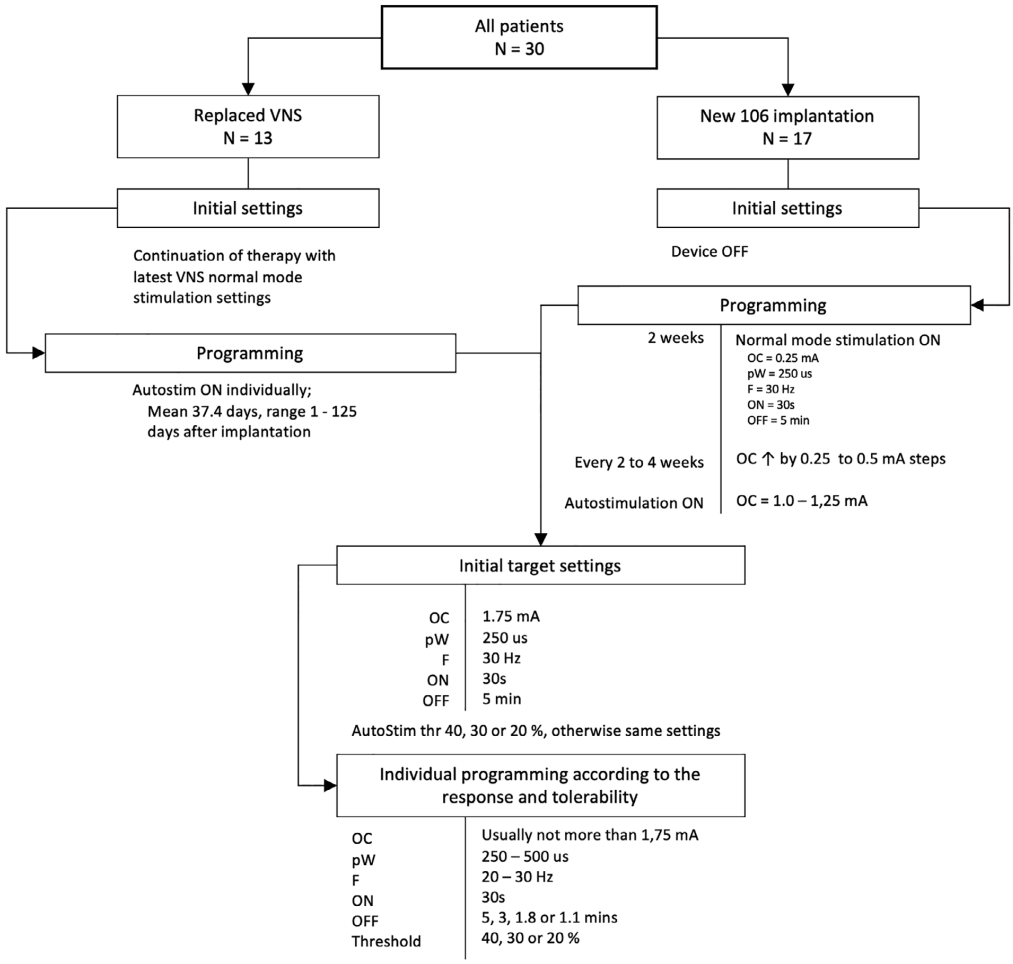


Figure 1 Patient groups and VNS programming scheme. Our study material consisted of replaced VNS and new implantation groups. In replaced VNS group of patients, the autostimulation mode was initiated according to individual consideration. In the new implantation group, we followed our programming protocol presented on the right side of the figure. The usual target settings and parameter ranges are presented. OC, output current (milliamperes); pW, pulse width (microseconds); F, frequency (Hertz); ON, ON-time (seconds); OFF, OFF-time (minutes); thr, autostimulation threshold rate, percentage.

The number of normal mode stimulations without rVNS in one day was calculated with a simple equation; the duration of a day was divided by a duration of a duty cycle, for example, the sum of OFF-time and ON-time. The number of normal mode stimulations with different OFF-times were the following: 5 minutes OFF: 262 stimulations/day, 3 minutes OFF: 411 stimulations/day, 1.8 minutes OFF: 626 stimulations/day, and 1.1 minutes OFF: 900 stimulations/day.

Electrical Charge

We used theoretical total charge (Q, Coulombs) in assessing the "VNS dose" as a quantitative value for the electrical charge delivered to the patients. For patients with normal cycling stimulation, the theoretical charge for one day was calculated with the formula for Q_{total} (17). When assessing total charge in rVNS patients, the formula is not applicable as the therapy time varied along with the altered number of stimulations. Therefore, we used the formula for t_{OFF} when calculating the Qtotal for rVNS patients (17,18). Four seconds added to ON-time represents the ramp time at the start and end of each stimulation.

$$Q_{\text{total}} = \left(\frac{T_{\text{period}} \left(\frac{1}{1000}\right) \left(\frac{pw}{10^6}\right) f (t_{\text{ON}} + 4)}{t_{\text{ON}} + (t_{\text{OFF}} * 60)} \right)$$

$$t_{\text{OFF}} = \frac{t_{\text{ON}} + 4}{\text{ON}\%} - t_{\text{ON}}$$

where Q_{total} is the total charge (C), T_{period} is the time period (sec), I is the output current (mA), Pw is the pulse width (msec), f is the

pulse frequency (Hz), t_{ON} is the ON-time (sec), t_{OFF} is the OFF-time (min). ON% = therapy time (%/100).

T_{period} is 86,400 seconds in this analysis, equals one day.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics version 23.0 was used. Since the data were not normally distributed, we used nonparametric tests. The corresponding values in different patient groups were analyzed separately to assess the *p*-values for significance. For two samples, we employed the Mann–Whitney test (later: M-Wt), and for several samples, the Kruskal–Wallis (later: K-Wt) test. In case of another group containing only one value, we utilized one-sample Wilcoxon signed rank test.

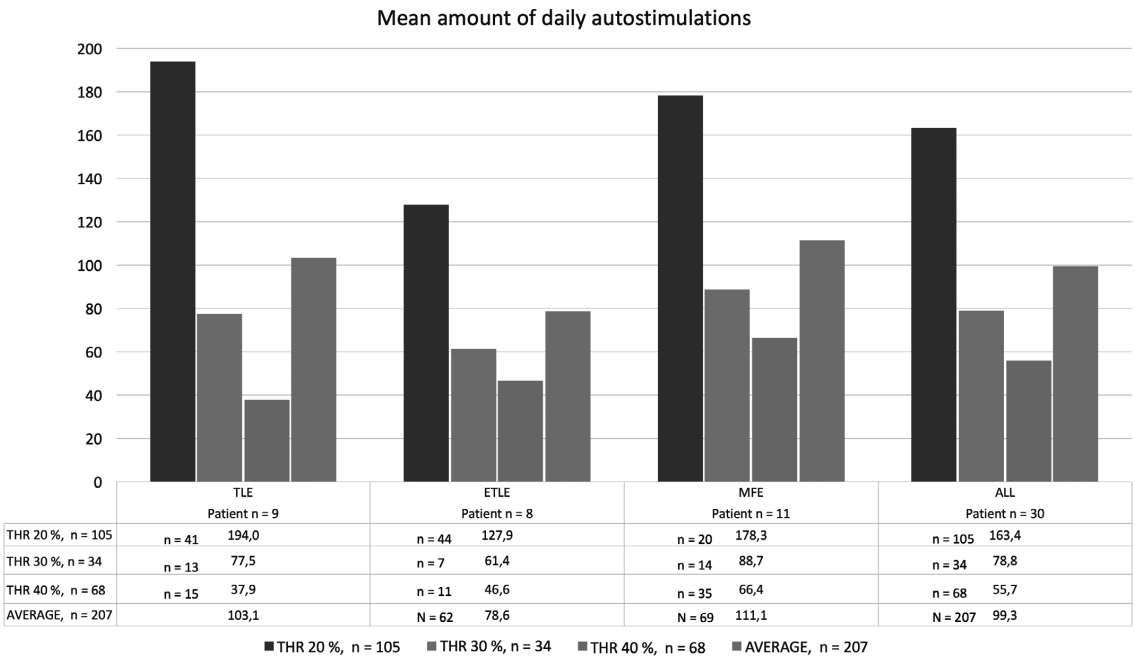
RESULTS

Patient and Follow-Up Data

Altogether 30 patients (19 women, 63.3%) were included in this study. A minority of the patients (*n* = 11, 36.7%) had intellectual disabilities. Age at VNS model 106 AspireSR implantation varied from 16 to 62 years (mean 34.7 and SD 10.59 years) and epilepsy duration at that point varied from 5 to 48 years (mean 24.6 and SD 12.49 years). Presurgical MRI was abnormal in 21 (70.0%) of the patients. Epilepsy types consisted of multifocal (*n* = 11, 36.7%), temporal lobe (*n* = 9, 30.0%) and extratemporal lobe (*n* = 8, 26.6%) onset epilepsies accompanied with a generalized epilepsy (*n* = 1, 3.3%), and an unknown onset focal epilepsy patients (*n* = 1, 3.3%). The predominant seizure type was focal impaired awareness seizures (*n* = 25, 86.7%) followed by focal aware seizures (*n* = 11, 36.7%), focal to bilateral tonic–clonic seizures (*n* = 10, 33.3%) and generalized tonic–clonic seizures (*n* = 1, 3.3%). A subgroup of patients (*n* = 13, 43.3%) received prior traditional VNS therapy. Reasons for battery replacements were battery depletion (*n* = 10, 76.9%), high impedance (*n* = 2, 15.4%), of which another patient also underwent a revision surgery due to a wound infection, and lacking efficacy (*n* = 1, 7.7%). All the patients in our institution are evaluated for epilepsy surgeries before the initiation of VNS therapy; only three (10%) patients experienced a surgery before VNS therapy.

The cumulative follow-up time for all patients was 14,778 days, that is, more than 40 years. Almost all the patients received rVNS stimulation with two or more (mean 2.5 and SD 0.82) different autostimulation thresholds with altered or unaltered OFF-times according to a preplanned protocol to optimize the treatment outcomes (Fig. 1). The duration of stimulation periods (SP) ranged from 1 to 352 days (mean 71.0, SD 57.4 days), for example, patients received stimulation with unaltered settings for the duration of the stimulation period. The average number of stimulation periods was 6.93 (range from 1 to 12) per patient. Individual follow-up time varied from 13 to 999 days (mean 492.6, SD 269.0 days).

The largest number of stimulation periods was within the five minutes OFF-time group (146 SPs) compared with the 3, 1.8, and 1.1 minutes OFF-time groups (30 SPs, 17 SPs, and 15 SPs, respectively). The mean OFF-time in different patient groups was



	TLE Patient n = 9	ETLE Patient n = 8	MFE Patient n = 11	ALL Patient n = 30
THR 20 %, n = 105	n = 41 194,0	n = 44 127,9	n = 20 178,3	n = 105 163,4
THR 30 %, n = 34	n = 13 77,5	n = 7 61,4	n = 14 88,7	n = 34 78,8
THR 40 %, n = 68	n = 15 37,9	n = 11 46,6	n = 35 66,4	n = 68 55,7
AVERAGE, n = 207	103,1	N = 62 78,6	N = 69 111,1	N = 207 99,3

Figure 2 Amount of automatic stimulations in different threshold rates according to the epilepsy type. Number for entries in the table is the number of stimulation periods. ALL-category also includes a patient with generalized epilepsy and a patient with an unknown seizure onset zone. THR, threshold rate for autostimulations; TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; MFE, multifocal epilepsy. [Color figure can be viewed at wileyonlinelibrary.com]

evaluated; in the new implantation group, it was 4.01 minutes (140 SPs, SD 1.51), replaced VNS group 3.76 minutes (90 SPs, SD 1.52), temporal lobe epilepsy (TLE) patients 3.85 minutes (70 SPs, SD 1.39), extratemporal lobe epilepsy (ETLE) patients 3.54 minutes (62 SPs, SD 1.63), multifocal epilepsy (MFE) patients 5 minutes (69 SPs, SD = 0.00), and in other patients 4.71 minutes (7 SPs, SD 0.76).

To monitor heart rate as accurately as possible, HB (heartbeat) sensitivity settings are defined individually. This process involves concurrent heart rate monitoring between the rVNS device and other medical devices simultaneously with different HB settings to find the most reliable setting. In our material, the HB sensitivity settings ranged from 1 to 5 (mean 2.70, SD 0.95), and the numbers were the following: n (1) = 4, n (2) = 6, n (3) = 16, n (4) = 3, n (5) = 1.

Effect of Autostimulation Threshold and Epilepsy Type on the Frequency of Stimulations

The effect of the autostimulation threshold and epilepsy type on the number of daily autostimulations is presented in Fig. 2. The threshold had a major effect on the number of autostimulations (p = 0.000, K-Wt) and the differences were the most pronounced with a threshold setting of 20% (p = 0.000, K-Wt). Moreover, in our data, the patients with TLE received the largest number of autostimulations, followed by MFE patients with similar numbers, whereas ETLE patients received less. To assess the significance, all the settings affecting the number of stimulations (OFF-time, ON-time, and threshold) were fixed to 5 minutes, 30 seconds, and 20%, correspondingly, by excluding the rest of the SPs. The results were statistically significant (p = 0.001, K-Wt), whereas TLE and MFE groups were similar (p = 0.487, M-Wt). The number of SPs in the analysis was 19, 10, and 16 SPs in TLE, ETLE and MFE groups.

The Effect of Stimulator Settings on the Frequency of Stimulations and Total Q

In order to analyze the additional effect of automatic stimulation activations on the total number of stimulations and energy consumption with different OFF-times, a dataset where all the other parameters were constant, was extracted. In Figure 3, the settings were the following: output current 1.75 mA, frequency 30 Hz, pulse width 250 µsec, ON-time 30 seconds, and the threshold for automatic stimulations 20%.

The amount of total Q (p < 0.0005), autostimulations (p = 0.002) and normal mode stimulations (p < 0.0005) increased whereas the share of autostimulations (p < 0.0005) decreased with shortened OFF-time (K-Wt). Initiation of rVNS in VNS therapy increased the total number of stimulations and total electrical charge if the rest of the settings stood unaltered. The result was significant with OFF-times of 5 minutes (p = 0.000), 3 minutes (p = 0.001), 1.8 minutes (p = 0.017) but not with 1.1 minutes (p = 0.068). As the compared group consisted of only one value, we utilized one-

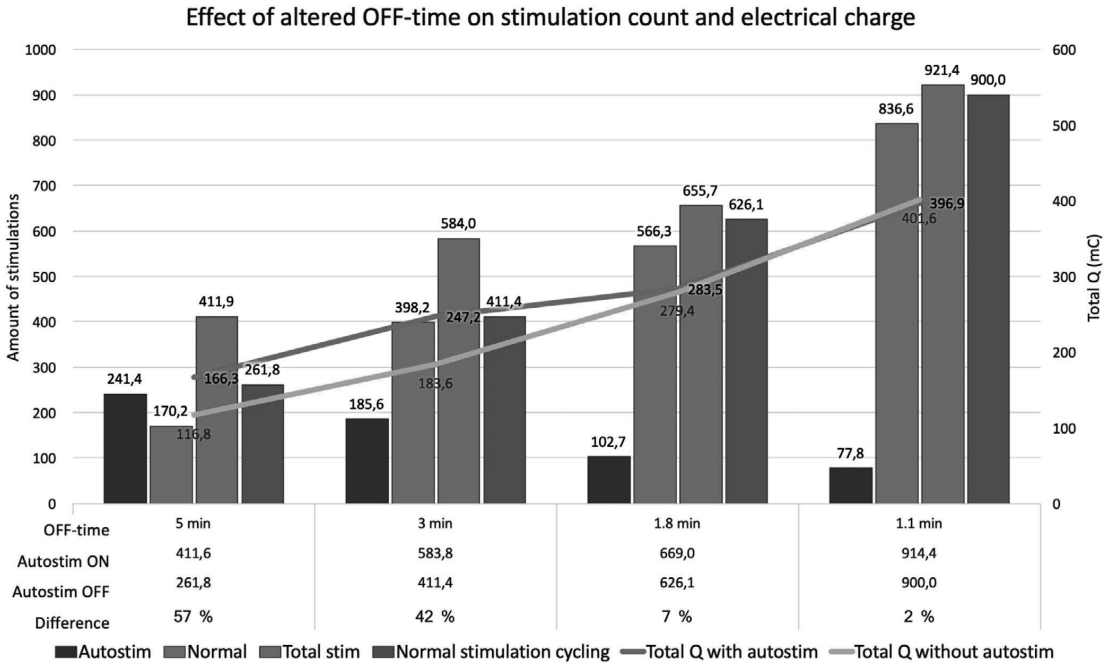


Figure 3 Effect of altered OFF-time on stimulation count and electrical charge. Only stimulation periods with 20% threshold were included. Shortening the OFF-time emphasized the dominance of cyclic stimulations. Regardless of the OFF-time, the initiation of autostimulation increases the number of total stimulations. Below the graph, the total numbers of daily stimulations are presented with the difference between the groups. The number of compatible stimulation periods for this analysis was 12 for 5-minute OFF-time, 5 for 3-minute OFF-time, 3 for 1.8-minute OFF-time, and 5 for 1.1-minute OFF-time. [Color figure can be viewed at wileyonlinelibrary.com]

sample Wilcoxon signed rank test. In the analysis, normal mode stimulation count without rVNS is computational with an assumption of not utilizing magnetic activations (Fig. 3).

In the group of five-minutes OFF-time patients, there were two outliers (number of SPs was 4 and 5) with significantly fewer autostimulation activations (mean 56, whereas the mean for the rest of the group was 241); patients with ETLE and TLE. These outliers have been excluded from the analysis. One of them have habitual tachycardia with a resting pulse of higher than 100 bpm. The other one have epilepsy due to a brain tumor leading for physically impaired condition and limited mobility. Due to these reasons, the variability in heart rate within these patients was distinctly different to the rest of the study population, and therefore the number of autostimulation activations was decreased. If they were included, the difference in the five-minutes OFF-time patient group between VNS and VNS with rVNS would have been 38%. If they had been included in the analysis, the change in the number and the share of the autostimulations would have not been significant ($p = 0.214$, and 0.462, K-Wt).

Additionally, a separate analysis of the patients with five-minutes OFF-time and 30 seconds ON-time was performed. The decrease of autostimulation threshold from 40% (57 stimulation periods) to 20% (40 stimulation periods) increased the number of autostimulations by 277%, decreased the number of normal mode stimulations by 24%, and increased the total stimulation count by 27% ($p < 0.0005$, K-Wt).

DISCUSSION

This study provides a detailed analysis of the autostimulation performance of responsive VNS therapy. Our material consisted of 30 patients with 208 stimulation periods as the basic unit for analysis providing a sufficient dataset for comparative analysis with the focus on stimulation periods with a five-minute OFF-time and 20% autostimulation threshold.

First, we described that the autostimulation frequency is highly dependent on the duration of the OFF-time and autostimulation threshold. Second, we demonstrated that the activation of the autostimulation mode had a major effect on therapy time and energy consumption with longer OFF-times (three and five minutes), and the effects were minor with shorter OFF-times. Third, we suggest that the epilepsy type might have an effect on autostimulation activation; in our material patients with TLE and MFE were more prone to trigger automatic stimulations compared with patients with ETLE. These findings may assist the programming of rVNS parameters, with special consideration of autostimulation performance and battery consumption.

The aim of this study was to quantify the differences in autostimulation activations in different OFF-times regardless of the cause for those differences. Our results show unambiguously that lowering the threshold rate for autostimulation detection leads to an increased number of autostimulations and a decreased number of normal mode stimulations, for example, shifting the balance from cyclic stimulation toward a larger share of automatic stimulations. A previous study shows a similar tendency in the number of automatic stimulations (9), demonstrating that the majority of automatic activations in rVNS therapy are not seizure-related. Moreover, a shorter OFF-time lead to a significantly higher amount of total stimulations and linearly decreased the share of autostimulations.

When using autostimulation mode, the total number of stimulations is self-evidently higher than using normal mode cyclic stimulation only. The difference and statistical significance was greater with longer OFF-times and the difference was not significant with 1.1 minutes OFF-time. Moreover, if the other stimulator settings are constant, the total energy consumption follows the total number of stimulations directly. Activation of autostimulation with five and three minutes OFF-times increased the total therapy time by 57% and 42%, respectively, whereas with 1.8- and 1.1-minute OFF-times the increases were 7% and only 2%, respectively. Therefore, the initiation of rVNS with 5- or 3-minutes OFF-times approximately doubles the therapy time when compared to traditional cyclic VNS therapy. Conversely, with shorter 1.8- or 1.1-minute OFF-times, the increase in therapy time with rVNS is minimal. The emphasis on predominant stimulation modality shifts from autostimulation-dominance to predominantly cyclic stimulation when OFF-time is decreased to 3 minutes or less. On the other hand, with briefer OFF-times there is less time for seizure-related detection; in previous studies, the median delay for autostimulation activations was 6–35 (9) and 8–50 (10) seconds after the seizure onset, depending on the used threshold setting. Moreover, patients with briefer OFF-times likely have more seizures as the cycling has been enhanced.

According to the traditional hypotheses, the efficacy of VNS therapy is based on direct and immediate (19–20), and indirect (21) effects of the stimulation. Indirect anti-excitatory modulation of neural circuitries is achieved after a longer duration of the therapy. The response to VNS therapy is progressively improving over time (5-6), supposedly due to the indirect effects of VNS. It has been hypothesized that the shift from constant cyclic stimulation to more variant stimulation patterns would lead to better responses.

In this technical study, we did not assess or examine the exact ratio of seizures to automatic stimulations. In all patients, the number of autostimulation activations greatly exceeded the number of seizures. Therefore, these nonseizure-related activations must explain the majority of autostimulation activations. There is recent data suggesting that the rVNS algorithm does not only detects seizure-related heart rate increases but also responds to rapid changes in cardiac sympathetic activations reflecting known circadian changes in autonomic function. Autonomic dysfunction is known to be present in patients with DRE both inter- and perictally (22).

CONCLUSIONS

The initiation of autostimulation mode in VNS therapy increased the total number of stimulations especially within longer OFF-times, and the purpose of this study was to quantify the differences regarding to the used stimulator settings. The number of autostimulations reflects either spontaneous heart rate variation or response to activity- or seizure-dependent changes in heart rate. Longer OFF-times were associated with a higher number of autostimulations. Temporal lobe and multifocal onset epilepsies triggered more autostimulations than extratemporal onset epilepsies. In this pilot study, we described performance characteristics of autostimulation mode in order to facilitate the understanding of parameter selection for rVNS therapy. The clinical significance of these characteristics should be addressed in further prospective controlled trials in larger and more homogenous patient groups.

Authorship Statements

Toni Kulju, Joonas Haapasalo, and Jukka Peltola designed and conducted the study including patient recruitment, data collection and data analysis. Toni Kulju prepared the manuscript draft with important input from Jukka Peltola. Joonas Haapasalo, Ryan Verner, Maxine Dibué-Adjei, Kai Lehtimäki, and Sirpa Rainesalo provided important intellectual help with writing and editing the manuscript to be ready to be published. All authors approved the final version of the manuscript.

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PUBLICATION IV

Circadian distribution of autostimulations in rVNS therapy in patients with refractory focal epilepsy

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Circadian distribution of autostimulations in rVNS therapy in patients with refractory focal epilepsy

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ABSTRACT

Background: Responsive vagus nerve stimulation (rVNS) utilizes an electrocardiograph (ECG)-based algorithm to detect rapid sympathetic activations associated with the onset of a seizure. Abrupt sympathetic activation may also be associated with nocturnal arousals between sleep cycles or transitioning from sleep to wakefulness, a period in which many patients with epilepsy experience seizures. Because of circadian changes in autonomic function, we hypothesized that the autostimulation feature might also behave in a circadian fashion.
Objective: The aim of this study was to assess the circadian rhythmicity of autostimulations in rVNS treatment in patients with drug-resistant epilepsy (DRE).
Materials and methods: We performed a retrospective follow-up study of 30 patients with DRE treated with rVNS including 17 new implantations and 13 battery replacements at a single center in Finland. After initiation of autostimulation mode, the exact rVNS stimulation parameters and the timestamps of all individual autostimulations delivered were registered. A clustered autostimulation was defined as any autostimulation that occurred within the duration of the therapeutic cycle during the therapy "OFF" time compared with both the previous autostimulation and the following autostimulation.
Results: Autostimulations and especially autostimulation clusters show a higher probability of occurring in the morning and less at night. This trend appeared to follow the circadian rhythm of cortisol concentration.
Conclusions: Early morning peaks of autostimulations at low thresholds may reflect awakening-induced activation of the cardiovascular system, which is associated with a shift towards the dominance of the sympathetic branch of the autonomic nervous system. Cortisol release occurs in parallel driven by wakening-induced activation of the hypothalamic–pituitary–adrenal axis, which is fine-tuned by direct sympathetic input to the adrenal gland. This is of interest considering the known sympathetic hyperactivity in patients with epilepsy.

1. Introduction

Epilepsy is a chronic neurological disease associated with frequent seizures that affect approximately 1% of the world's population [1]. While a number of pharmaceutical therapies exist for epilepsy, approximately one in every three patients does not achieve seizure freedom with antiepileptic drugs (AEDs) and requires nonpharmacological therapies such as resective surgeries, diet therapies, or device-based therapies such as vagus nerve stimulation (VNS), deep brain stimulation, or responsive neurostimulation (Neuropace) [2]. The criteria for drug-resistant epilepsy (DRE) are fulfilled when sustained seizure freedom is not achieved with at least two tolerated, appropriately chosen,

Abbreviations: ACTH, adrenocorticotropic hormone; AED, antiepileptic drug; ANS, autonomic nervous system; DRE, drug-resistant epilepsy; ECG, electrocardiograph; FBTC, focal to bilateral tonic–clonic; FDA, US Food and Drugs Administration; FLE, frontal lobe epilepsy; HPA, hypothalamic–pituitary–adrenal; HR, heart rate; HRV, heart rate variability; IGE, idiopathic generalized epilepsy; MFE, multifocal epilepsy; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy; rVNS, responsive VNS; SUDEP, sudden unexpected death in epilepsy; TLE, temporal lobe epilepsy; TWA, T-wave alternans; VNS, vagus nerve stimulation.

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1525-5050/

and used AED trials. According to the definition, AEDs can be used in combination or as monotherapies [3].

In 1994, VNStherapy received European approval followed by 1997 US Food and Drugs Administration (FDA) approval for DRE, with subsequent approvals expanding the base of indications for seizures and age ranges of prospective patients. In 2005, similar approval was granted for treatment-resistant depression.

Recent studies have begun to explore VNStherapy in chronic autoimmune disorders such as rheumatoid arthritis [4,5] and Crohn's disease [6] and other diseases with strong inflammatory components such as fibromyalgia [7]. It is possible that one of the likely multiple underlying therapeutic mechanisms is shared between all of these indications: chronic inflammation and autonomic dysfunction. Chronic inflammation and sympathetic hyperactivity are linked by a vicious circle, driving oxidative stress and multiple comorbidities such as heart disease and sudden cardiac death (SCD) [8]. Antiinflammatory therapies that pass the blood–brain barrier are known to be effective treatments for epilepsies that are resistant to typical AEDs. Specifically, adrenocorticotropic hormone (ACTH) therapies are known to regulate neurosteroid and melanocortin levels and have been shown to be therapeutic in DRE [9,10].

The vagus nerve is the key mediator of gut-brain communication and is critical in monitoring systemic inflammation. The nerve's afferent connections detect levels of inflammatory cytokines and transmit information about systemic inflammation to the hypothalamus, which in turn activates the vagovagal cholinergic antiinflammatory pathway, vagosympathetic antiinflammatory pathway, and the hypothalamic–pituitary–adrenal (HPA) axis. The vagovagal pathway corresponds to the vagus nerve's efferent connections, which are largely cholinergic and are believed to modulate an antiinflammatory pathway through nicotinic acetylcholine receptors, which in turn activate several cellular antiinflammatory mechanisms [11–14], in addition to modulating autonomic control of other organs such as the heart, lungs, and gastrointestinal tract. Furthermore, the vagosympathetic antiinflammatory pathway suggests that sympathetic efferent innervation of multiple organs via the greater splanchnic nerve can mediate a significant reduction in inflammatory cytokines [15–17]. In addition to these pathways, the HPA axis represents a slower hormonal response to long-term or circadian patterns of inflammation. Tracking the activity of the HPA axis can be done in a minimally invasive fashion by assessing serum cortisol levels [18], and cortisol levels are gaining attention as a circadian covariate with some seizure types [19].

Responsive vagus nerve stimulation (rVNS) utilizes a proprietary algorithm to detect rapid changes in cardiac sympathetic activations, which are associated with the onset of a seizure. This detection feature is then paired with a responsive stimulation mode which allows the rVNS generator to deliver an additional “dose” of stimulation, referred to henceforth as an autostimulation, which ideally contains spatial propagation of a focal-onset seizure thereby also containing the sympathetic cardiac consequences (ictal tachycardia and repolarization abnormalities) of the seizure [20]. Because of circadian changes in autonomic function, we hypothesized that the autostimulation feature might also behave in a circadian fashion. Thus, we collected autostimulation logs from rVNS devices in 30 patients in order to understand the underlying circadian patterns in autostimulation delivery.

2. Materials and methods

2.1. Patients

The study was retrospective and noninvasive, therefore, the approval of the ethics committee was not obligatory according to the Finnish Law on Research. All the patients were treated at Tampere University Hospital, Tampere, Finland.

Vagus nerve stimulation model 106 (AspireSR) was implanted to all patients between October 2014 and June 2017. According to our protocol, the VNS stimulation is usually initiated two weeks after the surgery, and the autostimulation feature is usually activated when the output current is set to 1.0 mA. During the ramp up, the output current was increased by 0.25 or 0.5 mA in every one or two weeks depending on tolerance. In the replacement VNS group, autostimulation mode was activated after the operation. After reaching the target current of 1.75 mA, the patients meet with a neuromodulation nurse usually once every 1 to 3 months. Depending on the frequency of the outpatient clinic visits, there might be gaps in data as the device overwrites the older entries when new ones are saved.

We have accurate follow-up data of autostimulations and other stimulator parameters. For automatic stimulation timestamp data, mean follow-up time was 13.1 months time per patient, ranging from 5.4 to 18.87 months. The cumulative follow-up time was 11,822 days, i.e., more than 32 years. Follow-up time has been counted as a time period between the first and the last saved autostimulation. Because of the limited amount of saved autostimulations, there are gaps in the follow-up. Downloaded autostimulation data with distinct stimulation parameters (such as autostimulation threshold and ON/OFF-time) were defined as a stimulation period. The total number of stimulation periods was 167. Most (24/30) of the patients had two or more stimulation periods with different threshold settings.

2.2. Autostimulation analysis

Downloads from rVNS device, containing timestamps of autostimulations, were analyzed in Matlab (MathWorks, Natick, MA) using custom software. These autostimulation timestamps contain information about the timing of the autostimulation detection trigger, whether or not therapy was delivered, and the heart rate (HR) detection threshold. The timestamps were first segmented by therapy delivery followed by the detection threshold. The maximum number of entries that can be downloaded from a single stimulation period was 3500. All data presented in this article represent autostimulation events where a HR change was detected and additional therapy was applied, and individual figure captions will define the detection threshold level of the displayed data (Fig. 2).

At this point, data were prepared for visualization of circadian rhythms by building 24-h histograms. Autostimulation timestamps were binned by an hour and normalized for display as bin probabilities over a 24-h period. Using this method, circadian trends were apparent but qualitatively weak (Fig. 1A). Further analysis of the fine-scale timing of the autostimulations indicated that “clusters” of autostimulations existed in the data and that a majority of the autostimulations occurred within tens of seconds to minutes of each other, with potentially hours between such “clusters” (Fig. 1B).

2.3. Autostimulation cluster detection

An autostimulation clustering method was defined with respect to each individual patient’s therapy in order to build a clinical definition of an autostimulation cluster as opposed to a mathematical definition. A clustered autostimulation was defined as any autostimulation that occurred within the duration of the therapeutic cycle during the therapy “OFF” time compared with both the previous autostimulation and the following autostimulation (Fig. 1C). Therapeutic “OFF” times varied between patients, but for a majority of patients, this duration was 5 min. Autostimulations that occurred in rapid succession within one duty cycle of therapy were believed to indicate insufficient delivery of therapy at a given time or representative of a systemic need for additional autonomic regulation. Following clustered autostimulation detection, nonclustered autostimulations were removed from the dataset, and 24-h histograms were prepared again (Fig. 1D).

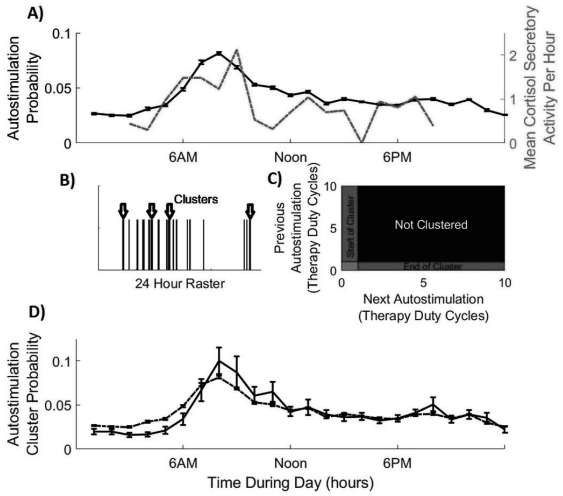

Fig.1. Classification of autostimulation clusters. A)Autostimulations from all patients were pooled in order to identify an average time course of autostimulation behavior over the course of 24 h (black). This trend appeared to follow the circadian rhythm of cortisol concentration (red [18]). B)Autostimulations are known to have high sensitivity but low specificity for detecting ictal tachycardia associated with seizures. As such, an algorithm was created to select for clusters of autostimulations that existed in close proximity to each other (arrows), which were believed to be more likely associated with a significant cardiac event. C)In order to select for autostimulations that were more likely associated with significant cardiac events, autostimulations which occurred in clusters that had less interstimulation interval than the generator's duty cycle were detected as a "clusters". The time between the previous (y-axis) and upcoming (x-axis) autostimulation was calculated for each autostimulation. Autostimulations which occurred within one therapy duty cycle from the preceding and following autostimulation were considered a member of an autostimulation cluster (green box). Autostimulations in the red boxes typically included not only the first and last autostimulations of a cluster but also instances of autostimulation doublets which were not included in our clustering definition. D)The autostimulations (dotted line) versus autostimulation clusters (solid line) show a higher probability of clusters occurring in the morning and less at night as compared with total autostimulations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

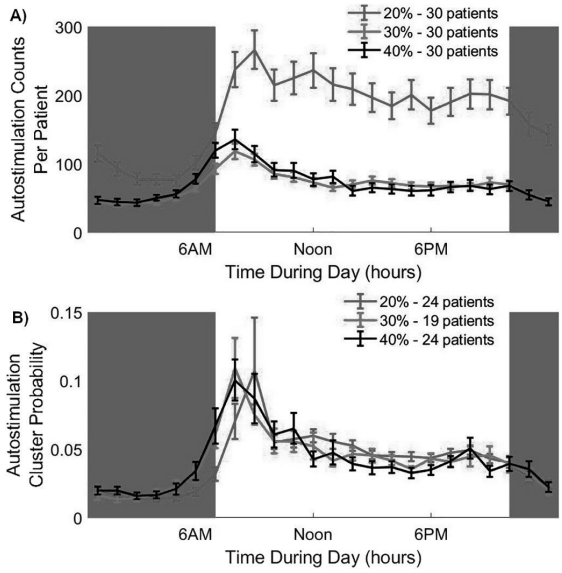

Fig.2. Cluster analysis excludes false positive detections at lower thresholds. A) Lower autostimulation threshold (20%) resulted in a high number of autostimulations per day, but the distribution of these autostimulations largely favored the daytime and specifically the morning hours. There was no significant difference in autostimulation profile between 30% and 40% detection levels. B)When clustering was conducted, all autostimulation cluster profiles were similar across the detection threshold. Thus, all detection threshold data were pooled for further cluster analysis. The shaded areas represent the nocturnal period. We did not collect sleep diaries.

2.4. Statistics

In cases where statistical analysis was performed in this dataset, 95% confidence intervals were calculated and compared between groups. The data included in these analyses contained autostimulation data derived from patients set to any threshold level for autostimulation detection as the clustering method efficiently excluded errant autostimulations and made the data from different threshold levels appear similar (Fig. 2).

3. Results

Thirty patients implanted with the VNS model 106 (AspireSR), i.e., rVNS device were included in this study. The mean age at rVNS implantation was 34.7 years (range: 16 to 62 years), and 36.6% were males. The mean duration of epilepsy at VNS implantation was 24.6 years (5 to 48 years). Seventeenwere new implantations, whereas 13 patients had received traditional VNS treatment before implantation of the VNS 106 device. Epilepsy types were classified into temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), parietal lobe epilepsy (PLE), occipital lobe epilepsy (OLE), multifocal epilepsy (MFE), and focal epilepsy with the unknown onset and idiopathic generalized epilepsy (IGE). In the analysis, we divided the patients into the following three groups:TLE, MFE, and ETLE (extratemporal lobe epilepsies). We tried to assess the circadian variation of the seizures, but our patient group was too heterogenous for meaningful analysis. All the patients were also treated with AEDs in addition to rVNS therapy. The majority of the patients had a combination of two or three different AEDs.

In our data, the cumulative number of autostimulations was 447,929 stimulations (average/patient: 12,106; median/patient: 12,977; range: 658 to 21,946 stimulations) that have been downloaded from the rVNS devices of all 30 patients consisting of 167 stimulation periods. The settings affecting the number of responsive stimulations were defined individually in each patient. In our programming scheme, we tend to aim for the lowest threshold possible to maximize the sensitivity and minimize the delay to react to seizures [21]. Heartbeat (HB) sensitivity setting of the rVNS device is defined by monitoring the HR with rVNS device and other medical devices simultaneously with different HB sensitivity settings to find the most reliable setting. In our material, the predominant HB sensitivity settings were the following: range: 1 to 5, mean: 2.70, standard deviation (SD): 0.95, $n(1) = 4$, $n(2) = 6$, $n(3) = 16$, $n(4) = 3$, $n(5) = 1$.

There was a clear circadian pattern in autostimulation activations independent of the used autostimulation threshold (Fig. 2). When the data were analyzed as seizure clusters, the cluster profiles in all three threshold rates were similar; the autostimulations occur the least during the night, the number increased substantially in the morning. This pattern resembles the circadian pattern of cortisol secretion (Fig. 1A).

Patients with TLE and MFE display similar patterns in circadian autostimulation activations (Fig. 3). Both TLE and MFE profiles display a strong surge in autostimulation cluster probability in the morning hours though patients with MFE appear to show a trend with more acute activation in the morning. The data of patients with frontal, parietal, and occipital lobe epilepsy were clustered into one group, patients with ETLE. In this group of patients also, the autostimulation cluster probability increases in the morning hours after the night although the data were too widely distributed for conclusions.

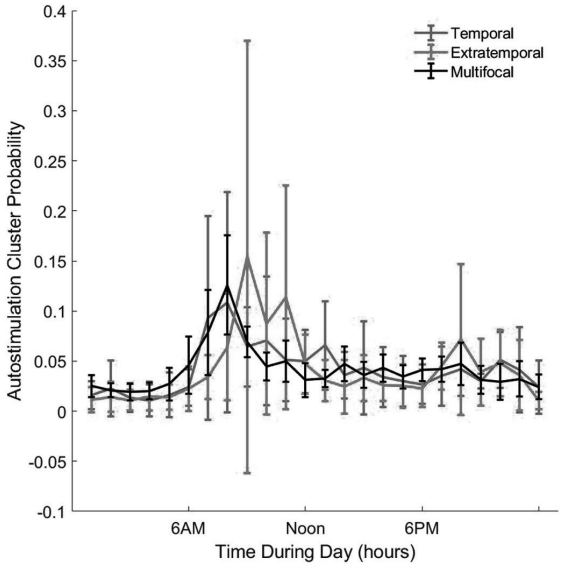

Fig.3. Temporal lobe epilepsy (TLE) and MFE display similar profiles of autostimulation clusters. Both profiles display an increase in autostimulation cluster probability reflecting a strong sympathetic surge in the morning hours though patients with MFE appear to show a trend with more acute activation in the morning. In the patient group with ETLE (comprising patients with extratemporal lobe epilepsy), the trend is similar although the data are too widely distributed for conclusions.

With battery replacement patients, the subsequent rVNS activation profile is similar to the profile of the rVNS patients without prior neuromodulation therapy (Fig. 4). In patients with prior VNS therapy, the peak in stimulation clusters during the morning hours trended to be more prominent.

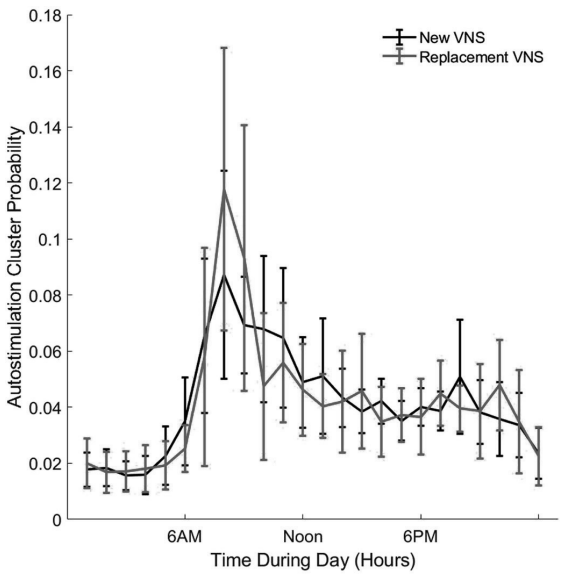

Fig.4. New versus replacement VNS therapy did not affect the profile of autostimulation clusters. Even in patients with many years of active VNS therapy, autostimulation appears to function similarly to newly implanted patients though replacement patients show a trend with more acute activation in the morning.

4. Discussion

This study demonstrates that rVNS delivered autostimulation clusters behave in a circadian fashion. The occurrence of autostimulation clusters is significantly higher during the time of morning wakeup, forming a similar pattern to the diurnal cortisol secretion. There were no significant differences in new implantation rVNS compared with the battery replacement group. These findings suggest that the rVNS algorithm which was designed to detect rapid changes in cardiac sympathetic activations associated with the onset of a seizure also reflects known circadian changes in autonomic function. This could indicate that responsive stimulation is serving a biological purpose beyond normal mode stimulation. Therefore, these autostimulation cluster activations may have both neuromodulatory and immunomodulatory consequences in addition to seizure response-related factors for patients with refractory epilepsy treated with rVNS.

Autostimulation cluster probability in our study appeared to follow the circadian rhythm of cortisol concentration providing interesting yet speculative neurobiological connotations. There are several different issues regarding the relationship between cortisol concentrations and epilepsy.The rise in brain cortisol levels leads to an increase in attention and vigilance [22]. On the other hand, stress is a known precipitant of seizures; stress hormones such as cortisol affect neuronal excitability and seizure threshold. The circadian rhythmicity of cortisol secretion with regard to seizure occurrence was evaluated in a systematic review; seizure occurrence showed a sharp rise in the early morning with a subsequent gradual decline similar to the rhythmicity of cortisol [19]. Moreover, the circadian variation in epileptic seizures is more common in TLE with seizures occurring predominantly between 9 PM and 9 AM but more during wakefulness [23–27]. The reported pattern of cortisol secretion resembles our findings of autostimulations.

The association between stress and increased seizure frequency seems to be undisputed, where the effects of stress hormones are mediated through fast nongenomic and slow gene-mediated pathways in several structures within hippocampal circuits [28,29]. Along with the clinical seizures, also interictal epileptiform activity is increased because of increased concentration of cortisol [30]. Some findings suggest that cortisol levels are elevated in patients with DRE with a reduction of these levels with VNS treatment [31]. This unbalanced situation is probably mediated by impairment in the negative feedback system of the HPA axis [32]. As the peak in cortisol concentration seems to decrease the seizure threshold while deoxycorticosterone and its metabolites increase it, stabilization of the corticosteroid system might have positive efficacy on patients with epilepsy [30,33]. There is a possibility that rVNS triggered autostimulations may counteract the harmful effects of unbalanced cortisol secretion in patients with refractory epilepsy [31].

Our results suggest that the rVNS algorithm does not only detect seizure-relatedHR increases but also responds to rapid changes in cardiac sympathetic activations reflecting known circadian changes in autonomic function. Autonomic dysfunction is known to be present in patients with DRE both inter- and periictally and can also be measured by measuring changes in HR. Heart rate variability (HRV) is the fluctuation in the time between the HBs, meaning the alteration in HR within a day. The ability of the heart to instantly accelerate or decelerate is an essential factor maintaining the homeostasis during sudden physical and psychological events. Heart rate variability can be used to study the integrity and flexibility of the autonomic nervous system (ANS). Rapid changes in HRV are usually mediated by central autonomic circuitry, whereas humoral factors affect the HRV more slowly [34]. As autonomic dysfunction and epilepsy have shown some correlation, low HRV and sympathetic hyperactivity can be considered as a risk factor for epileptic seizures. The increasing effect in HR and decreasing effect on HRV are especially high in bitemporal lobe seizures [35], while ictal tachycardia seems to be common in temporal lobe seizures [36].

Therefore, both cardiac manifestations of epileptic seizures and circadian variation in seizure occurrence seem to be more common in

TLEs [23–27,35]. These findings might be related to the association between ANS and the temporal lobes of the brain. Autonomic nervous system functions with the amygdala, which is part of the limbic system and an important autonomic nucleus for processing emotional reactions [37,38]. Furthermore, the vagal afferent network beyond the brainstem branches into three main pathways projecting to the thalamus, the amygdala, and the insula, which is in close contact with the temporal lobe [39]. The anatomical and functional associations between temporal lobes and the sympathetic branch of the ANS might partly explain the differences between TLE and other epilepsies even though in our study these differences could not be reliably assessed because of small sample size.

Moreover, autonomic dysfunction is suggested to increase the risk of sudden unexpected death in epilepsy (SUDEP). Even though the mechanisms leading to SUDEP are not yet fully elucidated, autonomic dysfunction might play an important role. Severe autonomic dysfunction as simultaneous sympathetic and parasympathetic hyperactivity along with postictal cerebral dysfunction is proposed to be involved in the pathogenesis of SUDEP [40–42]. Patients with increased sympathetic activity might be at a higher risk of SUDEP [43]. Therefore, especially focal to bilateral tonic–clonic (FBTC) seizures are a risk factor of SUDEP. There is also evidence of autostimulations preventing the propagation to FBTC seizures [44]. Thus, autostimulations might have a reductive effect on the occurrence of SUDEPs.

As SUDEP is considered a nocturnal phenomenon, our findings of circadian behavior of rVNS stimulations might have relevance with SCD rather than SUDEPs. Sudden cardiac deaths have long known to be more prominent in the early morning hours between 7 AM and 11 AM [45]. The risk of SCD among patients with epilepsy is threefold when comparedwith the general population, particularly in young women [46]. A recent review provides evidence that SCD may constitute an underrecognized cause of death in patients with refractory epilepsy [47]. Therefore, autostimulation in rVNS might help to reduce the incidence of early morning SCD by containing arrhythmogenic sympathetic discharge upon awakening.

Moreover, T-wave alternans (TWA) reflect repolarization abnormalities and are an established biomarker of cardiac mortality in patients with heart disease [48]. T-wave alternans increase with sympathetic hyperactivity have been shown to be drastically elevated in patients with refractory epilepsy [49] and to be significantly worse in patients with chronic epilepsy than in newly diagnosed epilepsy [50]. The reduction of TWA by VNS in patients with epilepsy was first reported by Schomer etal. [51] and later confirmed for rVNS by Verrier etal. [52], potentially reflecting a cardioprotective role of VNS.

There is some evidence from HRV analyses of VNS shifting the balance of the ANS towards parasympathetic dominance in patients with epilepsy with the effect taking place within the first six months but not improving further beyond the initial six months of therapy [53,54]. However, these effects of VNS on HRV are not unambiguous as other studies have found contradictory results, potentially caused by several crucial contributing factors such as used AEDs, age, epilepsy duration, seizure focus, seizure frequency, time of HRV measurement, and duration of analyzed epochs [55]. Furthermore, recent data suggest that response to VNS therapy may be predicted by the analysis of HRV. Liu etal. [56] measured interictal HRV before VNS implantation demonstrating that patients with higher parasympathetic or vagal tone (and higher HRV) were more likely to respond to VNS treatment. They also propose the tendency of patients having focal seizures to have a better response to VNS therapy than patients with mixed seizures. In their subsequent studies, they emphasize these findings [57] and suggest that VNS increases HR complexity [58].

Taken together, one may hypothesize that rVNS not only is triggered by sympathetic activations associated with seizures and with awakening but may also attenuate this known risk factor for morbidity and mortality by instantly increasing parasympathetic tone containing the autonomic deregulation. Considering the degree and high prevalence of sympathetic hyperactivity found in patients with DRE, further studies investigating the effect of rVNS on this comorbidity and its clinical impact are warranted.

5. Conclusions

This is a proof-of-a-concept study to assess the circadian distribution of autostimulations of VNS in patients with refractory focal epilepsy. We developed a concept of autostimulation clustering to maintain the ample amount of timestamp data to be able to format it to conclusions. According to our data, the circadian distribution of autostimulations seems to be similar to the circadian distribution of serum cortisol concentration. This study is not powered for a detailed analysis of epilepsy-related factors because of the sample size and diverse study population. In future studies involving a larger group of patients, the correlations between autostimulation, epilepsy, and humoral and autonomic neural factors reflecting human physiology should be addressed.

Declaration of competing interest

Toni Kulju has received grants from Maire Taponen's Foundation, Finnish Epilepsy Research Foundation, and City of Tampere Grant Committee. Ryan Verner is an employee of LivaNova PLC and holds stock options. Maxine Dibué-Adjei is an employee of LivaNova PLC and holds stock options. Sirpa Rainesalo has received speaker honoraria from Fenno Medical, Orion Pharma, and UCB. Kai Lehtimäki has received consultation fees and speaker honoraria from Medtronic and Abbott (former St. Jude Medical). Joonas Haapasalo has received support for travel to congresses from Medtronic and Stryker. Jukka Peltola has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for LivaNova, Eisai, Medtronic, UCB, and Pfizer. The remaining authors have no conflicts of interest.

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