NOTE

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Abstract

The aim of this proof of concept study is to investigate if an electronic nose (eNose) is able to make a distinction between breath profiles of diagnosed epilepsy patients and epilepsy-free control subjects. An eNose is a non-invasive device, with a working mechanism that is based on the presence of volatile organic compounds (VOCs) in exhaled breath. These VOCs interact with the sensors of the eNose, and the eNose has to be trained to distinguish between breath patterns from patients with a specific disease and control subjects without that disease. During the measurement participants were asked to breathe through the eNose for five minutes via a disposable mouthpiece. Seventy-four epilepsy patients and 110 control subjects were measured to train the eNose and create a classification model. To assess the effects of anti-epileptic drugs (AEDs) usage on the classification, additional test groups were measured: seven patients who (temporarily) did not use AEDs and 11 patients without epilepsy who used AEDs. The results show that an eNose is able to make a distinction between epilepsy and control subjects with a sensitivity of 76%, a specificity of 67%, and an accuracy of 71%. The results of the two additional groups of subjects show that the created model classifies one out of seven epilepsy patients without AEDs and six out of 13 patients without epilepsy but with AEDs correctly. In this proof of concept study, the Aeonose^{TM} is able to differentiate between epilepsy patients and control subjects. However, the number of false positives and false negatives is still high, which suggests that this first model is still mainly based on the usage of various AEDs.

1. Introduction

Epilepsy is one of the most common neurological disorders in terms of incidence and prevalence and it affects approximately 0.5%–1% of the world's population [1–4]. The disorder epilepsy is characterized by a predisposition to generate seizures that are associated with neurobiological, psychological, cognitive and linguistic problems [4, 5]. A seizure can be defined by a transient occurrence of signs and/or symptoms due to abnormal synchronization of neuronal activity in the brain [2, 5]. Seizures can occur randomly and in many patients a long period can pass in which there are no clinical signs present [2]. The initial management of patients with epilepsy starts with the understanding of the seizure type of the patient and, if pertinent, the epilepsy syndrome. The diagnosis of epilepsy after a first seizure is based on a combination of clinical information and different additional diagnostic tests, such as electro-encephalogram (EEG) and magnetic resonance imaging (MRI). Despite the guidelines for diagnosing epilepsy [6], the diagnosis of epilepsy after a first seizure is often complicated and time consuming.

EEG plays a central role in the diagnosis of epilepsy and could support the diagnosis of epilepsy or render it less likely. The duration of a routine EEG recording is approximately 30 minutes to one hour. Although presence of epileptiform discharge in the EEG recording supports the diagnosis of epilepsy, they are only recorded in 8%–50% [7] of the adult patients with a first seizure, which makes the sensitivity of the routine EEG limited [8]. The routine EEG can be repeated and sleep-deprived EEG can be recorded to increase the

chance of recording epileptiform activity [9, 10]. The combination of wake and sleep recordings increases the percentage of patients with clinically confirmed epilepsy to 80% [11] and thereby also increases the sensitivity of the EEG recording [9]. However, there are still epilepsy patients who do not show epileptiform activity in the repeated EEG recordings. Long-term EEGs can be recorded for a more reliable diagnosis, which is usually performed during hospitalization for one or multiple days. However, this is costly and stressful for the patient. A new diagnostic tool to diagnose epilepsy faster, more easily and with high sensitivity is in demand. Ideally this tool could also assist with determining the type of seizure when a patient arrives at the emergency department or whether a (change in) treatment is effective.

A recent paper demonstrated that trained dogs can detect the odour of an epileptic seizure with high sensitivity and specificity [12]. Over the last decades, several studies have been performed on the development of electronic noses (eNose) as a consistent and objective tool in the process of diagnosing e.g. lung cancer [13–15], Barrett's disease [16], head and neck carcinoma [13, 15], colorectal cancer [17], tuberculosis [18] and even complex regional pain syndrome [19]. An eNose is a handheld, non-invasive and easy-to-use device, with a working mechanism that is based on information related to volatile organic compounds (VOCs) in exhaled breath. These VOCs interact with the sensors of the eNose, and the eNose has to be trained to distinguish between breath patterns from patients with a specific disease and control subjects without that disease. After training, breath patterns from new patients suspicious of having the disease, can be classified based on comparative pattern recognition analysis [20].

Several studies have demonstrated a release of prototypical inflammatory cytokines as well as danger signal proteins such as High Mobility Group Box (HMGB1), and related signalling molecules in epileptogenic brain tissue [4, 21–23]. Potentially, these increased concentrations could be detected by an eNose and used for identifying specific epilepsy breath prints.

The overall aim of our project is to assess the relevance of eNose measurements in epilepsy with regard to establishing the diagnosis after a first seizure, determining the type of epilepsy when a patient arrives at the emergency department, and monitoring efficacy of (changes in) epilepsy treatment. The first step to achieve this overall aim is to train an eNose and create a breath profile indicative for epilepsy. Therefore, the aim of this first study is to investigate if an eNose is able to make a distinction between breath profiles of diagnosed epilepsy patients and epilepsy-free control subjects. This proof of concept study is the first study to use an eNose to detect a neurological disease.

2. Method

2.1. Participants

Patients diagnosed with epilepsy as well as control subjects without any suspicion of epilepsy were recruited. The breath prints of these two groups were used to train the eNose and to investigate if the eNose could distinguish between these two groups. Patients with epilepsy were recruited via the department of neurology and neurosurgery of Medisch Spectrum Twente (MST), the outpatient clinic of epilepsy centre Kempenhaeghe, and the EMU of the epilepsy centre Kempenhaeghe for patients on medication withdrawal, all in the Netherlands. Control subjects without epilepsy were volunteers accompanying patients visiting MST or Kempenhaeghe, and employees of both centres. Epilepsy patients were only included in the study if they were over 18 years old and if their diagnosis epilepsy was confirmed by a neurologist, regardless of their type of epilepsy, medication usage and seizure frequency. When patients were physically or cognitively unable to use an eNose, they were excluded from participation. The control subjects were included when they were over 18 years old, when they had no history of epilepsy or seizures, and when they were physically and cognitively able to use an eNose.

We assessed smoking behaviour, time since their last coffee and alcohol intake, comorbidities and current medication, as possible confounding factors on VOCs measured by the eNose. For the epilepsy patients, information was also obtained about their type of epilepsy and the time since their most recent seizure. All procedures conformed to the Declaration of Helsinki (amended version of 2008) and were approved by the Medical Research Ethics Committee Twente. All participants gave written informed consent prior to participation.

2.2. Materials

For the measurements we used the Aeonose^{TM} (eNose Company, Zutphen, the Netherlands). We had two devices that were used alternately at the two participating clinics. The Aeonose^{TM} consists of three micro hotplate metal-oxide sensors and a Tenax tube, which enable the recording of a breath pattern. During the measurement the metal-oxide sensors follow a temperature cycle profile. During this process, the sensors are exposed to the exhaled breath. On the sensor surface, redox reactions of the VOCs occur changing the conductivity of the sensor. On each sensor, the conductivity changes are recorded 64 times within the temperature cycle and the temperature cycle is repeated 36 times during one measurement. In this way an exhaled breath profile is recorded for each participant. A breath profile is based on the conductivity changes and does not show which VOCs are present in the exhaled breath during the measurement [20].

2.3. Measurement

Participants were asked to breathe through the Aeonose™ for five minutes via a disposable mouthpiece. The mouthpiece was placed in the subject's mouth and contained a high efficiency particulate arrestance filter which protects the Aeonose™ from contamination by bacteria and viruses. A nose clip was used to avoid nasal air passage and carbon filters were used to reduce the possibility that environmental VOCs would influence the measurement. During the first two minutes of the measurement the participant's lungs were flushed with clean filtered air that passed through the carbon filters. During the consecutive three minutes, a flow of the participant's exhaled breath passed the sensor surfaces and the Tenax tube. After five minutes of breathing through the Aeonose™, the Aeonose™ was set aside. During the remaining 10 minutes, VOCs locked to the Tenax tube were measured and the sensors were regenerated with clean filtered air. The total measurement time per subject was 15 minutes.

To avoid that classification of a breath profile is (partly) based on characteristics of environmental air at a specific location, the eNose measurements have been performed at three locations only: the outpatient clinic of the neurosurgery department of MST, the outpatient clinic of Kempenhaeghe, and the epilepsy ward of Kempenhaeghe. At each location, measurements were done in one room and equal numbers of epilepsy patients and their control subjects were measured to prevent environmental influence of the results of the classification.

2.4. Statistical analysis

For the data analysis of the Aeonose™ measurements the proprietary software package Aethena [18, 20] (the eNose Company, Zutphen, the Netherlands) was used, which took care of the data compression, data analysis and data reporting [19]. For each measurement 64 times 36 data points were recorded for each of the three sensors. In this way, each individual participant measurement consisted of a data matrix with thousands of records. These data were compressed using a Tucker3-like solution [20]. The resulting vectors of the compressed data points were entered into an artificial neural network (ANN). To train the ANN, measurements were pre-marked as either epilepsy or no epilepsy. Also, different scaling options and sensor combinations were used, creating multiple ANN options for separating epilepsy from no epilepsy. To largely ensure that the data was fitted to the VOC breath profile classifiers, data was cross-validated using the Leave-10%-Out method [20].

The results from the ANN breath profile that made the best separation between epilepsy and no epilepsy during the training were reported using the sensitivity, specificity and the accuracy. Accuracy was defined as the ability of the Aeonose™ to differentiate the patients and the control subjects correctly.

2.5. Influence of anti-epileptic drugs

Most epilepsy patients use anti-epileptic drugs (AEDs), therefore two additional groups of participants have been recruited to test the ANN epilepsy breath profile. The first group consisted of patients with epilepsy who had temporarily stopped using all AEDs, usually during their work-up for epilepsy surgery, and were recruited via the epilepsy centre Kempenhaeghe. The second group consisted of patients without epilepsy but who are using AEDs for neuropathic pain. These patients were recruited from the neurosurgery department of MST. The measurements of these two groups were indicated as blind measurements for the Aeonose™ and the accuracy of their classification was tested. The number of false positives and false negatives were reported.

3. Results

3.1. Participants

A total of 88 patients with epilepsy and 115 control subjects are included in this proof of concept study. From those 203 participants, 14 patients and five control subjects have been excluded due to shortness of breath or due to difficulties with the equipment during the eNose measurement. Additionally, seven patients with epilepsy who temporarily stopped using AEDs and 13 patients without epilepsy but with AEDs are included. The participant demographics are shown in table 1. The four groups differ statistically significantly from each other with regard to age. The epilepsy patients are statistically significantly older than the control subjects ($p = 0.01$). The test group of patients with AEDs but without epilepsy is significantly older than the other three groups ($p = 0.02$). Furthermore, there are more men in the epilepsy patient group than in the control subject group. Comorbidities most frequently reported are of cardiovascular (e.g. hypertension, arrhythmias), pulmonary (e.g. asthma) and neurological (e.g. traumatic brain injury, stroke) nature.

3.2. Training set

The results from the ANN breath profile are shown in table 2 and show that the Aeonose™ is able to make a distinction between the epilepsy patients and the control subjects with a sensitivity of 76% and a specificity of 67%. The overall accuracy in differentiating epilepsy patients from control subjects is 71% and 36 false positives and 18 false negatives are identified. The Receiver Operating Characteristics (ROC) curve of the Aeonose™ as a predictor is shown in figure 1. The area under de curve (AUC) is 0.77.

Table 1. Participant demographics.

	Patients with epilepsy with AEDs	Control subjects	Patients with epilepsy without AEDs	Patients without epilepsy with AEDs
Number of patients	74	110	7	13
Mean age (years ± SD)	46 ± 17	40 ± 15	36 ± 14	60 ± 16
Male (n)	42 (57%)	40 (36%)	3 (43%)	6 (46%)
Smoking: cigarette 1 h before measurement (yes)	11 (15%)	4 (3.6%)	0	3 (23%)
Coffee: intake 1 h before measurement (yes)	17 (23%)	18 (16%)	3 (43%)	1 (8%)
Epilepsy kind (n)				
Generalized	18 (24%)	—	1 (14%)	—
Focal	56 (76%)	—	6 (86%)	—
Number of AEDs (n)				
0	0	110	7	0
1	25 (34%)	0	0	12 (92%)
2	29 (40%)	0	0	1 (8%)
3	14 (19%)	0	0	0
4	6 (8%)	0	0	0
Mean duration epilepsy (years ± SD)	27 ± 19	—	20 ± 12	—
Most recent seizure less than 1 week ago (n)	26 (35%)	—	3 (43%)	—

Table 2. Results from the classification model based on the breath profiles of diagnosed epilepsy patients and control subjects.

Total number of participants	184
Epilepsy patients	74
Control subjects	110
True negative	74
True positive	56
False positive	36
False negative	18
# True	130
# False	54
% Error	29.3
Prevalence	$0.33 < 0.44 > 0.48$
Sensitivity	$0.64 < 0.76 > 0.85$
Specificity	$0.58 < 0.67 > 0.76$
Positive predictive value	$0.50 < 0.61 > 0.71$
Negative predictive value	$0.71 < 0.80 > 0.88$
Accuracy	0.71
Efficiency	0.71

3.3. Influence of coffee, alcohol and cigarettes

Several participants in the group of epilepsy patients as well as in the group of control subjects had consumed coffee or smoked a cigarette in the hour prior to the measurement. The intake of coffee or smoking a cigarette just before the measurement did not affect the classification of epilepsy patients and control subjects. There were no participants who consumed alcohol in the 8 h prior the measurement.

3.4. Influence of anti-epileptic drugs

The results of the two additional group of subjects show that the Aeonose™ classifies 1 patient with epilepsy without AEDs correctly, 1 patient as unknown, and 5 incorrectly. Six out of 13 patients without epilepsy but with AEDs are correctly classified.

4. Discussion

The aim of this proof of concept study was to investigate if the Aeonose™ can be used to make a distinction between patients with epilepsy and control subjects. To achieve this, an epilepsy breath profile was created. The results show that the Aeonose™ is able to make a distinction between epilepsy patients using AEDs and control subjects with a sensitivity of 76% and specificity of 67%. However, testing for the influence of the use of AEDs indicated that currently the medication usage has most likely a large impact on the generated epilepsy breath profile.

Several studies have shown that an eNose is able to detect lung diseases and cancer [13–18]. So far, no studies have been performed on detecting epilepsy with an eNose. With regard to diagnosing epilepsy, the EEG plays a central role. Specificity of EEG ranges from 78%–98% [11]. However, the sensitivity of the EEG is limited and it could be stressful for the subject. The sensitivity of the routine EEG ranges from 25%–56%. An additional diagnostic tool with a high sensitivity is desirable.

In this proof of concept study we studied how well the Aeonose™ could differentiate between control subjects and diagnosed epilepsy patients, prior to evaluating the value of an eNose in the diagnostic process. The results of merely detecting epilepsy with the Aeonose™ showed a higher sensitivity compared with the EEG in making a distinction between epilepsy patients and control subjects, but it should be noted that in our study all epilepsy patients had already been

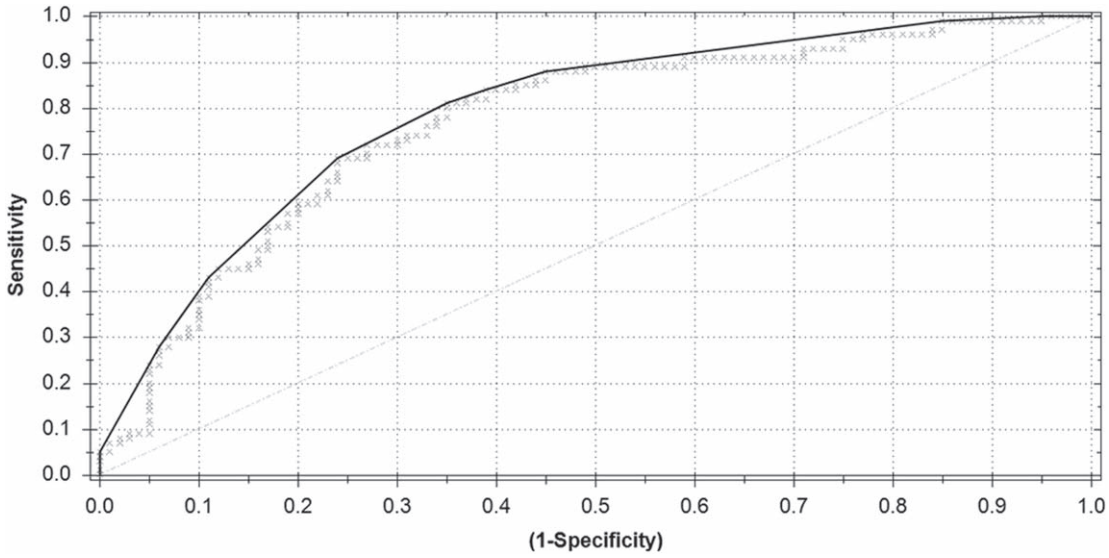

Figure 1. ROC curve of the Aeonose™ as a predictor of group: epilepsy patients versus healthy controls. AUC is 0.77.

diagnosed. This proof of concept study is the first step towards using an eNose in the process of diagnosing epilepsy. The advantage of the Aeonose™ compared to an EEG, is that the Aeonose™ is easy to use and to interpret.

4.1. Participants

There are statistically significant differences in age and gender between the four study groups. Dragonieri *et al* [24] investigated the influence of age and gender on breath profiles analysed with an eNose and according to their study the breath profile of healthy controls does not differ between age groups nor does gender has an influence [24]. However, earlier studies that used mass spectroscopy and gas chromatography to evaluate effects of age and gender on exhaled VOCs found specific differences between men and women [25, 26] or no gender specific differences but a significantly different alkane profile in older subjects [27]. Therefore, it cannot be fully excluded that group differences are responsible for classification errors. In future studies it could be considered to also use mass spectroscopy in parallel to the Aeonose™ measurements to learn more about the possible confounding factors. The sensitivity and specificity of the Aeonose™ in detecting epilepsy are still moderate and resulted in 18 false negatives and 36 false positives in the training set. This means that 24% of the epilepsy patients and 33% of the control subjects were classified incorrectly. There were no striking differences in the subject characteristics between the incorrectly classified participants and the correctly classified participants, for example, with regard to the comorbidities. However, according to table 1 only 35% of the epilepsy patients had their last seizure in the week prior to the measurement. The other 65% of the epilepsy patients were able to manage their epilepsy better with the use of AEDs. This could possibly lead to less differences between the epilepsy patients and the control subjects and subsequently possibly also to the number of misclassifications. No differences are found between the types and proportion of comorbidities in the epilepsy patients and the healthy subjects. This indicates that, in this proof of concept study, it has been difficult for the neural network of the Aeonose™ to detect patterns of epilepsy in the training set. The patients with epilepsy in our training set displayed a great heterogeneity with regard to their type of epilepsy, as well as their epilepsy severity, seizure frequency, time since most recent seizure and medication intake. Either a larger training set or a more homogeneous patient group could overcome this issue.

4.2. Influence of anti-epileptic drugs

All the epilepsy patients in the training set used AEDs while none of the control subjects did. This creates the risk that the breath profile characteristic for epilepsy patients that we found with the Aeonose™ is at least partly based on VOCs exhaled because of the AEDs and not exclusively because of their epilepsy. Majority of the patients used either one or two different types of AED. A post hoc analyses of the classification of the patients showed that there was no difference in the types nor number of used AEDs between the correctly classified patients and the misclassified patients. The same was the case for the time to last seizure. In addition, time to last medication intake could have influenced the generated classification model, but unfortunately this time has not been recorded.

To assess the influence of the AEDs in general we additionally included seven patients with epilepsy who had temporarily stopped using AEDs and 13 patients without epilepsy but who were using one or two AEDs.

These results show that the current breath profile generated by the neural network of the Aeonose™ classifies 60% of those participants incorrectly. From the seven epilepsy patients who had temporarily stopped using AEDs, five patients were classified incorrectly. This seems to favour the hypothesis that the breath profile generated by the ANN is mainly based on the usages of various AEDs. However, numbers are too small to come to a significant conclusion. Additionally, the epilepsy patients who temporarily stopped using AEDs were in work-up for epilepsy surgery. These patients are probably different in several ways from the patients whose epilepsy is relatively well controlled with one or two AEDs, and have different brain development and probably other comorbidities. Similarly, chronic pain patients who use AEDs probably also differ from the healthy subjects that were recruited to train the neural network. The difference is not only in the use of AEDs, but chronic pain patients also show changes in the central nervous system due to the chronic pain. Furthermore, chronic pain is often related with depression, anxiety, medication use and decreased physical activity [28, 29]. In a study of Bijl *et al* they showed that an electronic nose is able to make a distinction between patients with a complex regional pain syndrome and healthy controls. However, they did not take the use of medication in the different groups into account [19]. Nevertheless, the observed difference in the studied groups warrants further investigations.

To avoid the influence of AEDs in our future study, we will use the Aeonose™ in patients with a first seizure at the emergency department or in patients who are referred by their physician for suspicion of epilepsy. Those patients do not take AEDs yet and this is a patient category that would greatly benefit from a fast and easy diagnostic tool. Once they have received their diagnosis of epilepsy or no epilepsy, we feed their now labelled breath pattern to the ANN of the Aeonose™. This way we have breath patterns without AEDs of both epilepsy patients and control subjects and can be investigated how reliable the Aeonose™ can detect epilepsy and be used to assist with the diagnosis of first seizures.

Epilepsy affects approximately 0.5%–1% of the world's population. In our study, 40% of the participants were diagnosed with epilepsy. In our future study it would also be useful to investigate whether the same or a better accuracy is found in a study population that is more comparable to the general population, as accuracy is dependent on the prevalence of a disease in the studied population.

In this proof of concept study we have shown that based on a rather limited training set the Aeonose™ is able to differentiate between epilepsy patients and control subjects. However, the number of false positives and false negatives is rather high and there is a high risk that the use of AEDs has largely influenced the results. The Aeonose™ is an easy to use and well-tolerated device, that could potentially assist in the diagnosis of epilepsy, but adjustments in the measurements and extension of the dataset are needed to improve the generation of a breath profile indicative of epilepsy.

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