Bridging the epilepsy diagnostic gap: a fast, reliable and cost-effective rapid test (BREEDING)

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ABSTRACT

Clinical-grade EEG is immobile, expensive, and its interpretation relies on trained specialists. These requirements hamper the diagnosis of epilepsy as most affected people live in rural resource-poor areas where these diagnostic and clinical possibilities are scarce. In this project, we took up the challenging task to develop a rapid test technology prototype suitable for diagnosing epilepsy in a resource-poor setting. We established a key database and a first prediction model based on a deep learning algorithm, with similar diagnostic power as standard clinical EEG machines, but highly portable, affordable, easy to use, and without a clinical expert involved.

Keywords: Epilepsy diagnostics; EEG; image classification; global health

1. INTRODUCTION

Treatment of neurological disorders critically depends on proper diagnosis. Such diagnoses typically require face-to-face expert contact and high-cost examinations. One of the most burdensome neurological disorders is epilepsy, affecting at least 65 million young people, worldwide. The number of cases is twice as high in low-and-middle-income countries, compared to high-income countries, that is, 45 and 82 per 100,000 per year [1]. Even more concerning is that over 90% of people who suffer from epilepsy in low-and-middle-income countries remain undiagnosed and hence untreated. This is known as the epilepsy diagnostic gap. Limited diagnostic equipment and health care resources are key ingredients for the epilepsy diagnostic gap. In many of these countries acquisition of clinical-grade electroencephalography (EEG) connected to computer servers – a standard procedure in the diagnostic process – is not available. Clinical experts to interpret the EEG data are few and mostly concentrated in the larger cities [2]. Furthermore, interpretation of EEG recordings is challenging due to their non-stationary nature [3], the high inter-observer variation in clinical scoring, and the dependency on trained clinicians [4]. Lastly, EEG recordings require dedicated clinical recording rooms to overcome background noise, which further limits its applicability of diagnosis in less-privileged settings.

We established the technological essentials to potentially solve this treatment gap. Given the focus on supervised machine learning, we established an unprecedented database obtained at four independent clinical and community-based rehabilitation centers. This collected, standardized and labeled data contains resting-state EEG acquisitions and epilepsy diagnosis. This is a unique endeavor. The independent centers allow robust external validation with available training and testing data in children and adults with and without epilepsy.

Additionally, we initiated the development of a robust ImageNet-based epilepsy prediction model with only signature free resting-state data from as little as four electrodes as the input. The current predictive accuracy of the non-tweaked model is 0.64 on independent subject's data. These promising results indicate that automated diagnosis is likely, given that all input data was very carefully screened for the absence of epileptic background activity. In other words, manual raters – even by clinical experts – would not be able to diagnose epilepsy based on the model's input data, which yet contains 'hidden' diagnostic-relevant information. By collecting new data samples in the field at an early stage of the disease and augmenting the input data with non-selected EEG periods we will fine-tune the model towards maximal accuracy.

2. STATE OF THE ART

Currently, there is strong evidence that sensitive and specific diagnostic 'fingerprint' information is hidden within brain signals [5]. Based on that, the automatic classification of healthy personalized characteristics with EEG recordings in research environments has taken a

serious flight. In particular with the introduction of deep learning technology. Deep learning models are fruitful if sufficient labeled data is available to learn a hierarchical feature representation automatically. This includes features unnoticed by traditional techniques. Particular, of interest is the concept of information transference, where the central, generic layers of a deep neural network model are copied from elsewhere. This transfer learning has revolutionized convolution-based image models in multiple domains [6]. In this project we applied transfer learning by combining:

- The signal-to-image transformation of single one dimensional EEG recordings to two-dimensional brain-covering cross-correlation images.
- ImageNet transfer learning with cross-correlation images as input.

We also effectively incorporated the often overlooked problem of variable electrode placement in non-clinical EEG acquisitions using randomly selecting input channels from four brain areas. This uncertain placement issue is particularly important to tackle when using wearable EEG devices. Considering the recent interest in mobile EEG registrations [7].

3. BREAKTHROUGH CHARACTER OF THE PROJECT

To get beyond the current status quo of the epilepsy gap, we propose this technological breakthrough solution. We envision a future where the diagnosis of epilepsy is easy, fast, and straightforward. Our results do indeed suggest that this challenge is to overcome. We constructed the basis of a rapid test technology prototype, with similar diagnostic power as a standard EEG machine, but which is portable, affordable, easy to use, and presents the diagnostic evaluation within a couple of minutes by a virtual expert on a smartphone tablet or notebook (Figure 1). Besides, a deep learning algorithm is ideally suited to construct a 'stand-alone' rapid diagnostic test technology, as it allows for automatic feature extraction and full-window processing [8].

Such an automatic, human-expert-free, robust technology to diagnose individuals suspected of neurological disorders would significantly empower efforts to bridge the large diagnostic gaps. It would particularly help the most disadvantaged group of children and adults living with epilepsy: namely those in resource-poor and difficult-to-reach areas. Rapid test technology like we propose would in particular be very fruitful in community-based rehabilitation services. These dedicated services are suggested by the World Health Organization to ameliorate the serious problem of neurological disorders in low-and-middle-income countries [9]. Community-based services consist of local networks of trained community volunteers treating disorders such as epilepsy with cheap drugs and instructions for self-medication [10]. Currently, the most important bottleneck to unfold the full potential of these community-based services is the long, complex, and expensive process of diagnosis, requiring people living in remote places to travel multiple times to distant (and often expensive) neurological clinics and specialists [11]. We think that our project, providing diagnosis on the spot and elimination of the current time/effort bottleneck will facilitate fast upscaling of community services. This kind of rapid test technology is potentially feasible to fundamentally change the broad field of neurological disorders, as EEG is used in other (chronic) diseases as well for diagnosis and follow-up.

4. PROJECT RESULTS

The data collection process is depicted in Figure 2. Retrospectively data was collected from subjects referred to the outpatient First Seizure Clinic of the University Medical Center Utrecht, from 2008 and onwards. All had one or more paroxysmal events suspicious for epilepsy. Standard multichannel EEG was recorded, including resting-state periods. Epilepsy was diagnosed by a child neurologist based on clinical presentation, EEG findings, additional testing. All subjects had at least one year of clinical follow-up.

We acquired brain signals in people with epilepsy and healthy controls in a difficult-to-reach area in rural Guinea-Bissau (Oio province), Central Nigeria (Ebonyi State), and North Nigeria (Borno State). Five minutes of fourteen channel resting-state EEG data were acquired with a portable, wireless, low-cost consumer-grade EEG recording headset (EMOTIV). Acquisitions were done in standard home settings. The definite epilepsy diagnosis in the people suspected of epilepsy was determined utilizing seizure calendars during follow-up and used as gold standard data for model training. Healthy controls were recruited from the local community and families.

The current database contains in total 1547 entries: 981 labeled subjects with clinical-grade EEG and 566 labeled subjects with portable acquired, 'in the field' EEG. The distribution 'epilepsy' / 'no epilepsy' is ~4/6.

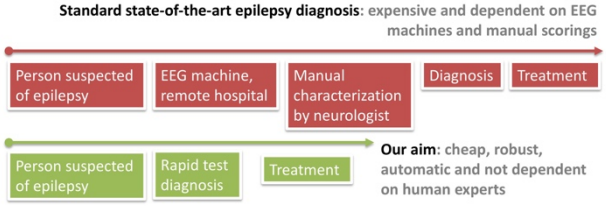

Fig. 1. The conventional workflow of epilepsy diagnosis involves expensive EEG machines and manual characterization of the acquired data (top). We aim to replace the clinical acquisition systems with a flexible wearable and automated diagnosis based on resting-state time-series.

Based on this unique database we have established a specific test case that is particularly difficult to diagnose, as least for a medical expert as the number of channels was reduced. From carefully clipped resting-state epochs

(~15 sec), free from any suspicious EEG characteristics, only data from four channels were kept after random channel sampling, to obscure the positioning (Figure 3). Data from 630 selected children (228 with epilepsy; 402 controls) were split at the subject level in a training and validation set (80/20%).

Within the deep-learning GluonCV mxnet environment a transfer learning Inception-v4/ImageNet classification model was fitted on the training set [12]. EEG signals were detrended, normalized, and converted to wavelet spectrum images (2-64 Hz), based on 100 random 224 ms signal snippets taken per resting-state epoch. Data augmentation included random crops and left-right flips. Batches of 70 images were fitted. The model performance on this rather difficult classification task is summarized in Table 1.

Tab. 1. Our ImageNet classification model performance. The Softmax cross-entropy loss measures the difference between the probability distributions (the lower the better) and is a measure of model fit. Accuracy is the ratio of the number of correct predictions over the total number of predictions.

Model characteristic	Performance
Training data accuracy:	0.65
Validation data accuracy:	0.64
Training data loss:	0.62
Validation data loss:	0.64

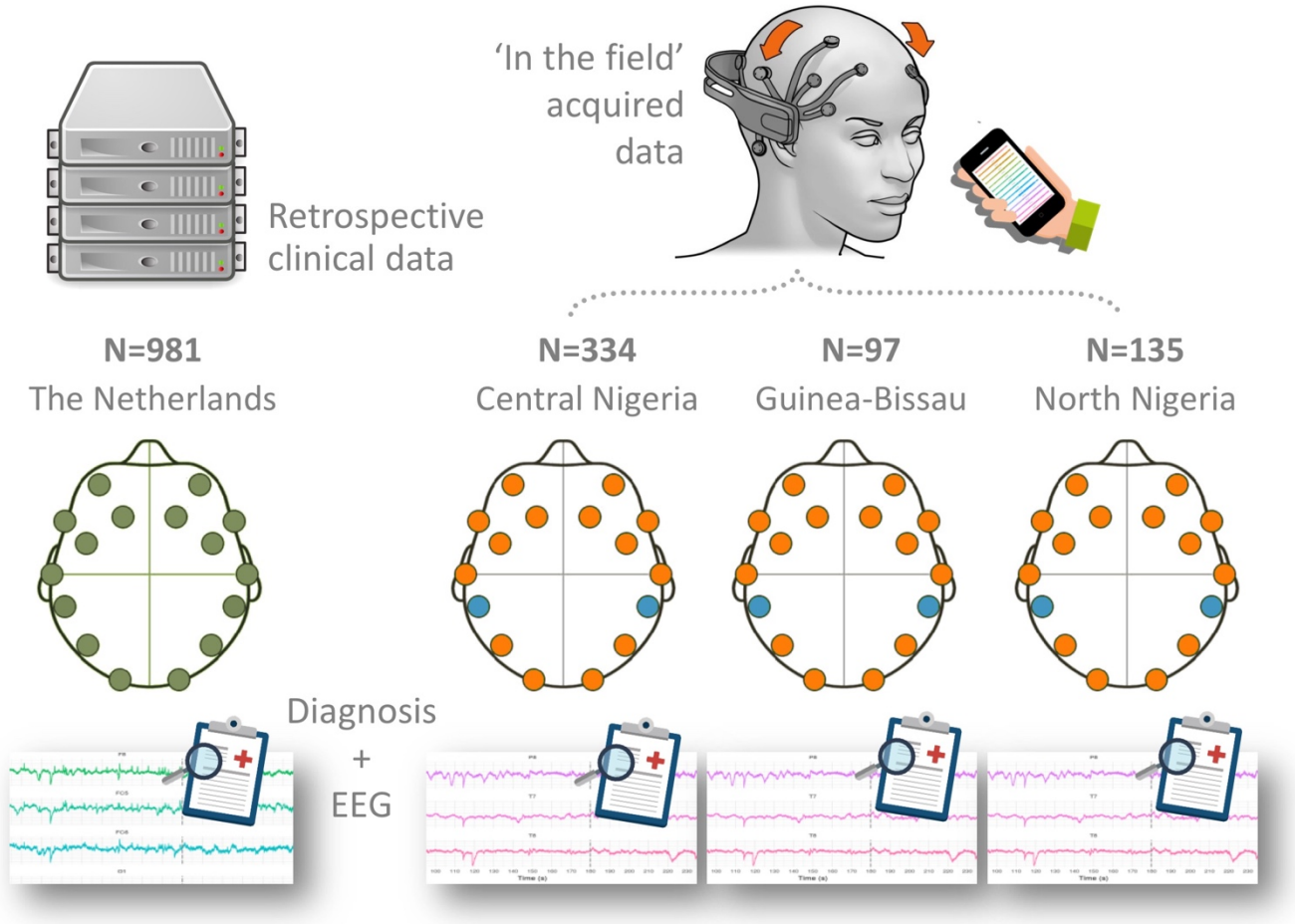

Fig. 2. A critical part of our project is the construction of a supervised machine-learning compatible database consisting of gold-standard clinical EEG resting-state recordings. In a retrospective manner all patients diagnosed in the last decade at an academic Dutch 'first seizure hospital' were standardized and labeled as 'epilepsy / no epilepsy' (left). Equally important are data acquired with mobile, 'in the field' sites, outside Faraday cages and prone to dust, background noise, and variable electrode placements. Therefore, resting-state EEG as acquired at community-based epilepsy services and clinical outposts in West-Africa in people with and without epilepsy (right).

5. FUTURE PROJECT VISION

Proper and sufficient data, covering the population at interest, determines whether a prediction-based technology will make the jump from the academic setting to the unruly practice of daily diagnosis in difficult-to-reach areas.

Our results create hope that low-cost brain recordings in combination with automatic time-series modeling may bring diagnostic capabilities to resource-poor settings. This hope also radiates towards the yet

unproven benefits of the proliferation of Internet and smartphone coverage in resource-poor settings. This automated technology has serious potential to increase health care access through so-called tele-neurology [13]. Cooperation with local partners is nonetheless essential for its success. We believe that our experience could be another step forward in this innovative field and may stimulate other contributions that may help to close the epilepsy diagnostic gap in regions where the burden of this disabling disease is highest.

5.1. Technology Scaling

The first four Technology readiness levels are mostly covered at the current level. After model fine-tuning, the technology could be readily validated in relevant community environments (TRL 5) and demonstrated in people with epilepsy (TRL 6).

5.2. Project Synergies and Outreach

Our current consortium is a unique combination of both academic hospitals and community-based services. This allows rapid switching and interactions between lab and clinic. In ATTRACT Phase 2 we will reinforce our consortium through collaborating with other Phase 1 funded projects and international initiatives, which have much more expertise on transfer learning and deep neural net models. Rapid model development is possible given the available database.

5.3. Technology application and demonstration cases

The second phase of this project will boost the applicability of personalized medicine in neurological disorders. Most importantly, it will provide an alternative to the traditional face-to-face diagnosis in neurological settings. The end-to-end rapid test technology will stimulate scientific and industrial innovations using optimized dry sensor brain acquisition with strong yet accurate signal classifiers that do not require user knowledge on feature selection and do not depend on special noise-free recording environments. Direct societal impact will be found in the field of global health diagnostics and tele-medicine. This simple and accurate rapid test will be a game-changer in bridging diagnostic neurological gaps in low-and-middle-income countries. For instance, a similar rapid test may be developed to predict the prognosis of children with cerebral malaria. The impact reaches beyond neurological conditions in low-and-middle-income countries. Our rapid test – with software that potentially allows fast synchronization through the Internet – will significantly accelerate the progress in tele-neurology in European society. Neurological consultation at a distance is currently an evolving branch of innovative tele-medicine. It has far-reaching implications for the future practice of medicine and the way that providers deliver care to their patients with headaches, dementia, epilepsy, stroke, movement disorders, and multiple sclerosis.

Our rapid test prototype perfectly fits within this exciting, yet highly unexplored research field. Our project will demonstrate that conventional neurological care is not always the most efficient or convenient way to consult and provide care to neurology patients. The accurate and automatic classification of such a complex disorder as epilepsy with our rapid test will alter neurological care and open avenues towards the delivery of remote care. Our rapid test is thus a very timely development given the increasing demand for neurologic services in a growing population also in high-income countries.

Our prototype technology can be a very effective way to extend the patient to reach and develop tailored and personalized neurological follow-up using remote recordings. It is paramount that practitioners maintain high-quality care, equivalent to traditional in-person visits. Working with open hardware and software is therefore critical and will directly benefit the Research Infrastructure communities in Europe.

5.4. Technology commercialization

Valorization of our technology is possible. The surge in medical tele-devices currently seen in both high and middle-income countries indicates that commercialization is timely and perfectly fits within the rapid increase of smartphone use in low-income countries. Even in the difficult-to-reach areas. Standard outpost clinics and private general practitioners all around the globe are therefore a potential sales area. We have spoken with Utrecht Holdings, which invests in promising start-ups. They are very interested and suggest to work on a minimum viable product.

5.5. Envisioned risks

The core risks that our project will face in a potential ATTRACT Phase 2 project is the uncertainty of increasing the diagnostic accuracy to clinically-relevant levels. We expect that this tool will already be useful if accuracies beyond seizure calendar detection power are found in unseen subjects, given the detrimental effects of epilepsy and the significant disease burden. Perfect accuracy is not required to select clear epileptic subjects. Our database comprises data from four independent centers. This allows robust cross-validation. In our difficult test case, a non-optimized ImageNet model showed accuracies clearly above chance. We expect that fine-tuning and incorporation of more than four channels will mitigate this risk.

Liaison with Student Teams and Socio-Economic Study

Four students from TU Delft and Erasmus University took the opportunity in the CERN IdeaSquare summer school 2020 to work on the technology in our BREEDING project. They formed a team and were supervised by one of us (EvD). Their pitched project movie on portable EEG acquisition is available here.[1] The student pitch was well received but the judges did not find it feasible enough in the current state of technology to deem it the winner. What became clear from the interaction with the students is that the global health perspective and the importance to diagnose epilepsy is a strong incentive to work on such a project. Receiving valuable input and innovative ideas from talented master students with a different background (i.e., industrial design, space engineering, economics, and mathematics) made us aware of the pluripotent character and the challenges of our project. We, therefore, will persuade to continue to work together with Master and PhD candidates for input, either as a project or by joining university hackathons.

6. ACKNOWLEDGMENT

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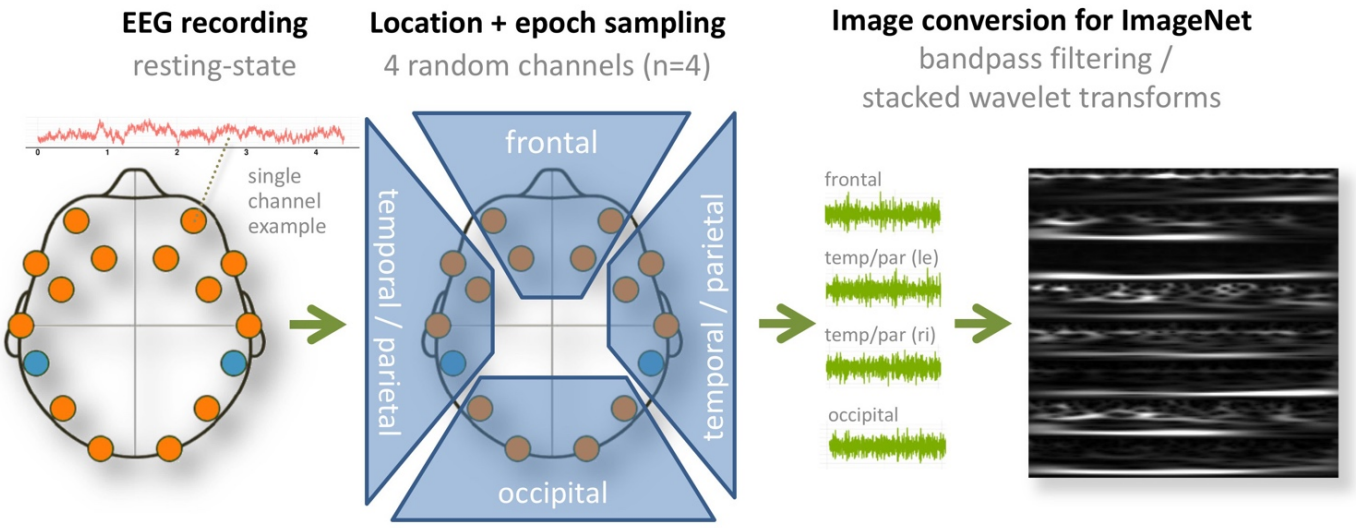

Fig. 3. The pre-processing pipeline of our brain-wide location-insensitive EEG modelling is schematically depicted from left to right. Standard located resting-state EEG recordings are randomly sampled in sets of four electrodes, originating from the frontal, occipital and temporal/parietal skull regions. Within a temporal window, free of any visible epileptic activity, random sets of 224 ms epochs were sampled, bandpass-filtered between 2–64 Hz and characterized as wavelet transformed cross-correlation power spectra between the four selected channels. The four stacked power spectra generate a 224×224 image, ready for an image-based neural network.