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Alternative Point of View: Development of a Novel Task-Based fMRI Brain-Mapping Protocol for Deaf Epilepsy Patients

Part A – Applicant

A.1 Applicant

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Part B – Scientific proposal

B.1 BASIC DETAILS

B.1.1 Title

Alternative Point of View: development of a novel task-based fMRI brain-mapping protocol for deaf epilepsy patients.

B.1.2 Abstract

About 30-40% of all epilepsies are drug-resistant and require alternative solutions. A subset of people has epilepsy as well as hearing impairments. Epilepsy surgery is considered an option only after a risks and benefits evaluation. This evaluation starts with functional brain mapping, where one of the popular and widely available neuroimaging techniques is functional magnetic resonance imaging (fMRI). Unfortunately, current fMRI protocols for epilepsy patients strongly rely on audible communication, which is not an option when evaluating patients that have audible impairments or are deaf. Therefore, the current complexity of pre-surgical evaluation procedures leads to lower chances for non-hearing patients' candidacy for epilepsy surgery. This proposal will address this challenge.

Previously conducted studies suggest that uncontrollable seizures have effect on structural brain connectivity, which, in combination with differences in audible input processing, make it harder to obtain a reliable brain mapping. Therefore, this research proposes the (1) development of an alternative scanning protocol, suitable for deaf epilepsy patients. Additionally, to further investigate inter-patient neuroplasticity in deaf individuals, we aim to recruit healthy deaf volunteers to perform functional task-based and resting state scans via 7T MRI scanner. As a result, (2) a dataset of high-resolution will become a groundwork upon which we can develop a better understanding of pathologies in deaf patients. Moreover, obtained data will be used to (3) critically revisit previously proven functional regions of the brain, employing newer and updated connectome mapping tools, like diffusion weighted imaging (DWI).

B.1.3 Layman's summary

The unpredictable and uncontrolled burst of recurring electric brain impulses in people with epilepsy significantly worsens the quality of a patient's life. There are various types of epileptic seizures - the incidence, duration, and nature of which greatly differ. A search for an effective medication can take years. After 3-5 different unsuccessful drug treatment attempts, the patient is considered a candidate for implantation of a neurostimulator or surgery. While medication helps to reduce the occurrence and severity of seizures, surgery aims to completely cease them and help patients gain back control over their lives. However, the surgical candidates are rather a small and thoroughly chosen group. Pre-surgical evaluation starts with the localisation of critical white matter pathways and functional regions, responsible for speech, auditory, visual, motor functions etc. The current most popular non-invasive tool is functional magnetic resonance imaging (fMRI), which can be resting state (assessing overall functional brain connectivity) or task-based (localising function associated with the given task). It is a non-ionising neuroimaging method, which can be done on MRI machines of different strengths (1.5 T, 3 T, 7 T), according to a protocol dedicated to epilepsy. By asking a patient to perform certain cognitive tasks, task-based fMRI allows visualising which region of the brain fires up in response to a requested task. However, it is more difficult to identify which brain regions correspond to functions in deaf patients because (1) language areas are often shifted or relocated; (2) prolonged seizures lead to microstructural and functional alterations; (3) sound-based fMRI tasks are not possible. That is because deaf people communicate through the means of sign languages. Therefore, we need an alternative pre-surgical evaluation method for deaf community representatives.

In this project, we focus on the development of a task-based fMRI brain mapping method that relies on a safe visual stimulus processing protocol that avoids epilepsy-related visual triggers (flash) and prioritises patients' safety. Therefore, this project starts with the development of an alternative protocol for adult healthy deaf volunteers. We will apply this task two times per individual with two months' time in-between (to map consistency and reproducibility). To minimise deviation within the dataset, we will only hire prelingual (hearing loss occurred in infancy, prior to learning how to speak) deaf people who have the Dutch sign language as their mother tongue. Obtaining data of such kind will be ground-breaking and it is in our interest to investigate the variability of functionally mapped brain locations in deaf people while focusing on the investigation of language centres. Moreover, the developed visual task-based fMRI scanning protocol for deaf people can be further adapted for other pathologies and disabilities.

Functional connectivity and brain mapping partly rely on the underlying anatomical brain configuration. Studying the anatomical brain configuration of healthy volunteers that are deaf will help to further characterize the identified functional language areas and prove if they are differentiating from hearing individuals. For that, we will also revisit the previously proven neuronal connections utilising connectomics analysis tools (like diffusion-weighted imaging) and analysis techniques (like weighted graph comparison). Revisiting textbook examples is a brave step, however, that would contribute towards the reduction of uncertainties around neurovariability in cognitive and anatomical profiles of healthy deaf people.

To summarise, the main expected outcomes of this study are (1) a novel visual task-based fMRI scanning protocol for deaf people, also suited for deaf epilepsy patients; (2) an openly available dataset of deaf peoples' brains, containing high-resolution structural and functional information with high grades of consistency and reproducibility; (3) proof of language area shifting and relocation in prelingual deaf individuals; (4) proof that epileptic seizures have a structural and functional impact on the brain connectivity.

B.1.4 Keywords

Epilepsy, prelingual deafness, pre-surgical brain mapping, language area localisation, functional magnetic resonance imaging, diffusion-weighted structural imaging.

B.2 SCIENTIFIC PROPOSAL

B.2.1 Research topic

Background (B.2.1.a)

In 2020 about 50 million people were affected by epilepsy [1]. It is a functional neurological disorder, which is often diagnosed by examining the excessive neuronal activity in the cortex with the use of an electroencephalogram (EEG) [2]. After that begins a search for an optimal pharmacological treatment, which is able to reduce the occurrence of seizures in 60-70% of all cases [3]. The trials and adaptation to switching between medications might take years, during which patients' condition and quality of life can significantly worsen [4]. In the case of refractory epilepsy (which means medicament resistant) dietary restrictions, neurostimulation and surgery are proposed as alternative solutions. Although surgical intervention is associated with high risk and potential post-surgical complications, it also has a high (68%) chance of remission [3]. Most of the refractory epilepsy cases get referred for surgery, however, only about half of the patients will be operated on. Aiming to predict the chances of successful surgical outcomes, pre-surgical evaluation is carried out. The surgery is aiming to remove as much tissue as possible without causing disabilities and deficits in brain cognitive functions. The minimum necessary amount of brain tissue that should be removed to prevent seizures is called the epileptogenic zone (EZ) [5,6]. Localisation of EZ and crucial functional centres are the main objectives of non-invasive brain mapping. Pre-surgical planning aims to find out the most efficient ways to preserve them.

One of the biggest challenges in epilepsy treatment is accurate brain mapping: identifying the essential functional cortical brain areas, which need to be spared during surgery at all costs, as removal will render the patient handicapped. Next to motor function, language comprehension and performance are essential. Surgical planning procedure in deaf epilepsy patients is troublesome as current protocols strongly rely on audible tasks to map the language areas. This evaluation is obviously not possible for deaf epilepsy patients, since prelingual deaf people communicate and think in a visual language. In The Netherlands, the Dutch sign language has officially been recognized as a true language in 2020 [7]. Mapping these visual language areas is important and potentially possible through visual stimulation. However, when working with epilepsy patients, additional precautions should be considered in the task as visual cues, like flashes, may trigger seizures. Also, large variations in language areas are expected in this patient group. There is strong evidence that the auditory cortex adopts the functions of the visual processing cortex due to the neuroplasticity, shifting functional processing of major specialized brain areas to distant locations. The auditory cortex is also most commonly removed during epilepsy surgery (namely the part of the temporal lobe). More generally, recurrent epileptic seizures impact the structural organisation of the brain. This structure is an important constituent of the functional brain connectivity that characterizes the synchronization within functionally related brain areas.

To provide the necessary amount of background information for a fuller understanding of the topic, firstly, the complications related to currently available neuro-mapping methods will be discussed.

Brain mapping has been previously done with intracranial EEG or Wada (intracarotid amobarbital) testing, which had limited availability due to being a very invasive procedure that required prolonged patient hospitalisation [1, 4, 8, 9]. However, nowadays that is a lastly considered option and non-invasive solutions are prioritised. More modern non-surgical options include Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) [10, 11]. In comparison, PET scanning procedures are slower, more expensive, and less available in a clinical setting and results do not provide the desired resolution. The wide clinical availability of MRI machines makes it a tool of choice for non-invasive brain mapping.

Functional Magnetic Resonance Imaging (fMRI) is a standard neuroimaging instrument, which helps to detect structural and functional brain changes [12]. There are two types of fMRI and the key differences between them dictate what can be visualised. The resting state fMRI (rs-fMRI) is obtained in the absence of stimulus and can visualise chronic seizure-related changes, while a task-based approach (tb-fMRI) localises neuronal activity emerging from cognitive or sensorimotor tasks [12, 13]. Studying epilepsy helps to locate EZ and language centres. If during the pre-surgical evaluation, clinicians discover a risk related to these areas, the patient often gets denial in resection surgery [14]. They are essentially recognised by tracking differences in hemodynamic responses, which is done by the means of measuring regional changes in oxygen supply and cerebral blood flow [13, 15]. BOLD stands for blood oxygen level-dependent contrast imaging and is used to conduct functional brain maps from the measured fluctuations of neural activity [15, 16]. Changes promoted by blood flow and metabolism will be detected as a distinction in the intensity of a few per cent (0.5-5%) [12]. Differences between oxygenated and deoxygenated blood can be visualised due to the variation in magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin [13]. Having an idea about the underlying processes behind brain mapping and risk assessment surgery is important to understand why this research is needed and how it can be done efficiently. In the development stages of a study design, deciding on better ways to acquire and analyse data can save time, which is pressing in healthcare.

Patients are scanned according to epilepsy-specific fMRI protocols. The most recent guidelines propose Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS) protocol, the technical details of which will be discussed in the next sections of this proposal [1, 17]. The rs-fMRI has been prevalently chosen for patients with disabilities and conditions that might make task implementation difficult. That is also the case with epilepsy patients. However, in a clinical investigation, it is hard to determine solely from an rs-fMRI why are the observed abnormalities present [18]. Because rs-fMRI does not provide insight into the functionality. Additionally, previous studies have expected epilepsy to be a functional disorder, resulting in little to no gross abnormalities on structural images, however, more recently conducted ones strongly suggest otherwise [19, 20]. Sometimes a combination of neuroimaging technologies is used, like EEG and MRI. However, it is challenging to capture EEG signals simultaneously, while performing MRI, since the magnetic field gradient pulsations lead to large currents in electrodes. That can degrade the quality of obtained MRI data due to the contribution to RF noise [21]. More recent technologies manage to implement ways to combine these modalities without noticeable disadvantages. However, it is also important to consider that these modalities provide complementary information, which is acquired differently. For example, seizure localisation is done within the temporal resolution in EEG and in spatial resolution when looking at MRI scans. Developing a reliable method to combine multi-modally acquired data is a key step in predicting surgical outcomes with a necessary amount of certainty.

Therefore, it is simpler and more reliable to perform brain mapping in epilepsy patients with the use of tb-fMRI. However, classical epilepsy protocols strongly rely on audible inputs and communication with the patient [14, 22]. Standard tb-fMRI epilepsy protocols for hearing individuals can be examining semantic judgement, language lateralisation, story comprehension and verbal fluency [14, 18]. And the stimulus materials provided to the patients are audible and visual. That leads to the conclusion that standard protocols cannot be executed for the deaf patient brain mapping; therefore, the verbal/audio communication for this group of patients should be substituted with an alternative method. The development of this new method for deaf healthy patients is a complex problem for various reasons, the main of which are individual structural variation and altered regional functionality due to neuroplasticity [23]. This method is not yet available.

This research, therefore, proposes the development of an alternative brain-mapping method for deaf and deaf epilepsy patients, which will rely on visual stimuli. The second group is not at all common, so it would be harder to find the necessary number of participants. However, it is not uncommon for Dutch hospitals to get in touch with patients and request a contribution to science in a form of study participation. A proposed method is based on translating the existing audio test into Dutch sign language, such that the task is fully compatible with non-hearing individuals. The data collection will start with scanning deaf healthy volunteers. Having obtained a dataset of healthy deaf individuals following the same protocol provides a strong baseline, which allows for direct comparison between healthy and epilepsy deaf patients. Application of this method to deaf epilepsy patients is even more delicate due to potential visual triggers. However, the development of the alternative task-based fMRI protocol, suitable for deaf epilepsy patients, will not only allow studying the impact that seizures have on brain structural integrity and functionality but also increase the chances of this patient group getting surgical treatment for epilepsy with a higher certainty of a positive outcome.
The difficulty will be described in the paragraphs that follow, along with a promising mapping technique that could help to resolve it.

Due to limiting factors for the use of tb-fMRI, the chances for representatives of this group to be accepted for the surgery are generally smaller. Deaf patients' participation in the described evaluation procedure (brain mapping) can only happen if the current protocol will be modified. During the acquisition time, the patient is required to stay still in the scanner, while deaf peoples' communication depends on gesticulation and the use of sign language and some parts of the assessment might require communication with the clinicians. And even then, it is challenging to distinguish which brain part is being stimulated since their communication relies on gesticulation through sign language. For example, if a patient would struggle to respond, it could be because of the interference affecting muscles, vision, comprehension, ability to understand the question etc. To perform such evaluation it is, however, important to understand that in able-hearing patients motor and language-related areas are mapped during the pre-surgical planning. That is done to know which areas to avoid during the surgery since it would have a big impact on the patient's life, if those areas get irreversibly affected or removed. However, deaf patient communication depends on different skills (visual recognition, gesticulation etc) and also the brain areas, which are commonly responsible for the processing of audible stimuli, are functionally different due to the neuroplasticity properties. To summarise, in deaf people, the aim is to map the regions, which are crucial for their communication and this task is complex because there is not enough research performed and data gathered about this particular patient group. This highlights the need to modify the currently available scanning procedure. For example, switching the audible description of the task to the video, which would contain a sign language interpreter instructing the deaf person on which button to press. There are currently available MRI machines, which allow patients to see the screen while being positioned in a scanner. More about this will be explained further, in the section of this proposal describing the approach. We believe that with enough preparation and implementation of modern technologies, tb-fMRI scans will be available for deaf people with little to no distinction in the acquired results.

Therefore, it is more difficult to identify EZ and language centres in deaf epilepsy patients. Some studies show that differences in auditory experiences might affect the morphology of brain networks in deaf adults. A prolonged sensory limitation often leads to the reorganisation of the brain structures and related functionality due to the compensation of neuroplasticity [24]. It also matters if the patient has prelingual or acquired deafness [5, 25]. Previously conducted studies show that prelingually deaf people have higher network clustering and nodal efficiency than a control group of able hearing, while the group with acquired deafness almost does not differ from healthy controls [23]. The modification of auditory cortex functionality in deaf people makes it process visual and touch stimuli instead [2]. This is due to the adaptability of the brain. Moreover, structural changes between prelingual deaf and healthy able-hearing patients are expected, but high anatomical intra-patient variability makes it difficult to predict the exact differences in functionality related to the same areas. This research question is trying to solve a complex issue. It is, therefore, important to break it down into smaller aims and focus on one task at a time. Our hypothesis is based on the fact that we want to investigate the common changes in brain structures conditioned by epilepsy-related impact and audible deprivation. This is expanded by the awareness about the structural variability per patient. The hypothesis is that the prelingual deaf individuals' brain has adapted to the limitation in auditory processing, resulting in some inter-patient co-occurring similarities. To prove this, the allocation of language regions in deaf epilepsy patients should be compared to deaf healthy volunteers. We should also choose a method to precisely quantify such deviations. Studying the anatomical brain configuration of healthy volunteers that are deaf will help to map the extent of lateralisation. This information directly impacts how much cortex is being removed from the temporal cortex during the surgery.

The inter-patient differentiation in the deaf epilepsy patient group is additionally complicated by the presence of seizures, tumours and other brain abnormalities. Previously conducted studies show that over time uncontrollable seizures have an effect on structural brain connectivity, which makes it harder to predict a positive surgical outcome [14]. The exact locations of centres corresponding to functions (like speech recognition, auditory processing, and visual comprehension) greatly vary from anatomical books even in healthy able-hearing volunteers. There are inter-patient sources of variability, which should often be considered when searching for brain connections. Neuroplasticity: the brain changes and adapts to the smallest physiological changes (like lack of sleep or too much caffeine). To eliminate additional sources of variability and make the experiment more reliable, these details should be communicated to the patient groups beforehand and documented during the acquisition. Most of the studies investigating brain connectivity focus on structural region interconnection [23, 26]. However, that knowledge is not enough since epilepsy is a functional disorder. Additionally, the causal relationship between seizure propagation and regional modification of functional responses has yet not been proven [12]. That creates a knowledge gap in the understanding of epilepsy in deaf people. A more insightful overview of systems functioning can be obtained by reviewing the connectome. The evaluation of network organisation can be investigated with different techniques. As an example, the diffusion MRI (dMRI) tractography method will be described below. However, it is important to highlight that dMRI is not the only proposed or best method for this research. This investigation aims to solve a complex problem and finding out suitable visualisation and data analysis tools are part of the research question.

Diffusion MRI tractography is a method based on the differences in diffusion anisotropy of the tissues [27, 28], which allows to investigate white and grey matter, as well as to assess the spatial connectivity of neuronal connections. Depending on the anatomical composition and cell characteristics, water molecules tend to move more easily along axonal fascicles as a result of molecular diffusion. The white matter tracts in the brain exhibit maximal diffusivity due to their directional dependency, which also enables the viewing of these tracts in 3-dimensional (3D) pictures with colour coding. To obtain diffusion-weighted data, participants will undergo MRI scanning using advanced sequence settings. The dMRI sequences should be added to the scanning protocol, which would extend the scanning time, however, it is not expected to be causing a significant delay. It is convenient in terms of this research because data collection for both patient groups will be performed on MRI scanners and obtaining dMRI data does not require additional resources or preparations. Defining the most efficient way to perform the scans can be a part of the research question. Doing prior research on novel data analysis methods can help to choose which settings should be prioritised. For example, by obtaining multiple shell data, we are able to do constrained spherical deconvolution (CSD) and increase the chances for data interpretation [29, 30]. Defining scanning protocols is always a trade-off between scanning time and data quality.

CSD is a powerful higher-order tractography method, which performs estimations from acquired multiple fiber populations, despite the fact that it has unique data requirements. Computational improvements and acquisition artefacts limit the mapping of microstructural brain components. In digital imaging, the smallest 2-dimensional(2D) unit is a pixel and in 3D - voxel. However, one voxel typically represents multiple tissue types and hence multiple diffusion directions. This is also connected to the crossing fibers phenomenon and the partial volume effect, which leads to false positive predictions or premature abortion of fiber tracking [29, 30, 31, 32]. The research team's ability to accurately investigate the data strongly depends on their capacity to develop a viable DWI model, which will provide data estimation and description. This danger is minimised by the involvement of CSD in the model estimation procedure. Therefore, the preferred technique for the proposed investigation is CSD.

To perform the abovementioned data analysis technique, an additional sequence should be added to the MRI scan planning (multi-shell data acquisition). That also gives room for testing out other various techniques within the dMRI domain. When planning a research project, it is important to consider the machines available within the institution as well as their availability. In the case of the abovementioned DWI methods, MRI scanners will be exploited. Even though a sufficient amount of detail can be obtained with the use of 1.5 T and 3 T MRI scanners, recent studies highlight the advantages of high-field 7 T MRI scanning [10]. It has been recently approved for clinical use and allows us to judge microstructural tissue connections and functionality based on a more sophisticated amount of detail. For example, the presence of cortical dysplasias, which were previously undiscovered on 3 T scanners [33]. Therefore, the use of a high field 7 T MRI scanner is preferred, however, can be adjusted depending on the project planning and hospital equipment availability during the set timeframe. More suggested methods are described in the approach part of this proposal.

Additionally, there is an expected amount of uncertainty that continues to exist within the field of neuroscience. Science, like any other industry, has its own trends and popular movements, starting from favourable methods for post-mortem sample preparation. Techniques change as science advances; however, certain discoveries do not get second-guessed and cross-examined. Some of the recently published papers highlight the need to revisit already proven correlations of brain pathways and functions with new tools for connectomics analysis [12, 33, 34]. It highlights the advantages of predicting surgical outcomes, which can be achieved if inter-patient connectomics variability will be studied more extensively with novel technologies. It also mentions differences in the obtained results, conditioned by the chosen methods. The systematic review in question suggests dMRI tractography, as it has proven to be a reliable non-invasive method with high sensitivity [12, 35]. The study also proposes associating the analysed tract regions with more than one function. Differentiation in functionality depending on an observed hemisphere is mentioned to be often overlooked, and therefore, could be revisited. This would provide a better understanding of how regional impairments influence cognitive performance or lack of its functionality.

In conclusion, these are the issues, making task-based fMRI brain mapping in deaf epilepsy patients a complex problem:

(1) different functional organisation of language areas due to variation in sensory input processing;
(2) different structural appearance of language areas due to neuroplasticity;
(3) the impact of epileptic seizures resulting in structural changes in the brain tissue;
(4) potentially outdated anatomical information regarding brain connectivity.

Overall aim (B.2.1.b)

The aim is to create an improved non-invasive brain-mapping method, which can help to localise the functionality of language areas in deaf epilepsy patients.

This will be done by developing a protocol, which would allow to efficiently scan patients with hearing disabilities. Those scans provide brain mapping, which is an essential part of the pre-surgical evaluation. Finding a way to overcome epilepsy-related impact and audible deprivation-dictated differences would allow us to perform a structural brain connectivity assessment. Developing a scanning protocol for deaf epilepsy patients will increase the chances for this patient group to be considered for surgery. Moreover, critically revisiting previously proven functional regions of the brain with newer and updated connectomics analysis tools will be beneficial not only for studying deaf brain neuroplasticity but can be later used as a baseline to research other pathologies in the deaf community.

Objectives (B.2.1.c)

This overall aim is unravelled in three more specific objectives:
1) to develop an alternative visual task-based scanning protocol, suitable for deaf people and deaf epilepsy patients.
2) to investigate inter-subject neuroplasticity in deaf individuals.
3) to construct an open-access high-resolution multimodal dataset to characterize the interplay between epilepsy and deafness on the network architecture.

B.2.2 Approach

General study details

The study is mainly divided into three subcomponents:

(1) alternative visual task-based fMRI protocol development for deaf people;
(2) data collection of healthy adult volunteers with prelingual deafness;
(3) brain connectivity research.

The problem is divided rather broadly and can be subdivided into more specific paradigms later in the research. A schematic representation can be seen in figure 1 (page 10).

This project is planned to work with two separate groups –deaf non-epilepsy (otherwise healthy) volunteers (DHV) and deaf epilepsy patients (DEP). It starts with the development of visual methods to perform task-based fMRI in deaf people and data collection of DHV. The third step is data preparation, which is anonymization to secure volunteers' details and pre-processing to improve quality. Once the data set is ready, it will be released to the general or scientific public. Additionally, to the improvements to the current fMRI procedure in the group of interest, the expected outcome of this step is a groundwork upon which further research on structural brain connectivity in deaf people can be done. One of the additional (complementary) aims of this project is also the establishment of collaborations and data sharing. This would be very beneficial for the study, considering that cooccurrence of deafness and epilepsy is rare: only a couple of cases per year in The Netherlands. Optimisation of the previously acquired data for deaf epilepsy patients would allow for the revision of the currently used protocols and improve procedures. Moreover, it is not unusual for Dutch hospitals to reach out to particular patient groups when testing new technologies. And we are aiming to develop alterations to the current standard epilepsy patients' protocol, which can be then utilised in the hospitals.

The next stage of the project is data analysis, which is rather split into language region localisation and investigation of brain connectome. It includes the localisation of language centres in deaf individuals' brains, in comparison to hearing individuals. The language area shift or relocation is expected. This step also includes critically revisiting previously proven information about brain region functionality. Data will be obtained on a 7 T MRI scanner, so reviewing widely accepted information with improved tools can reveal something new. Once the visual procedure to acquire a deaf epilepsy patient's task-based fMRI is organised and scans are acquired, those can be compared to a tb- fMRI scans of the deaf healthy volunteers.

Recruitment Approach

In the ideal study design set-up, a total of 150 adult prelingually deaf participants would have been recruited. The proposed minimum sample size was deduced from Faul et. Al's G* Power3.1 method and corrected according to the sample size guide by Machin [36, 37]. However, the number of people with both refractory epilepsy and deafness is very small. In this study, we, therefore, firstly focus on the population which is more prevalent: deaf people without epilepsy, but with their language areas shifted. So, the DHV group size can still be 75, while the other group will be significantly smaller due to the rare co-occurrence of deafness and epilepsy. So the initial participation of the 75 deaf epilepsy patients will be lowered and dictated by the number of patients in this group at the time of the research. The data collection step in this study group was planned to be executed in the later stages of the project. The number of participants required for scanning will be further verified during the literature review stage to be completed in the first year of this project. In case of an inability to contact the necessary amount of participants for the DEP group, there is a backup idea that can be developed further. Substituting DEP group with non-deaf epilepsy patients to characterize the effect of recurrent seizures on the structural elements.

Deaf healthy volunteers will be primarily and consensually recruited through the patient base of University Medical Center Utrecht. In terms of this research, we focus on prelingual deafness cases and to minimize intra-group variability in the beginning stages of project development only these patients will be contacted. They will be provided with all the necessary information, precautions, and scan-related limitations prior to the first scan. The same task will be applied again for each patient within two months' time, aiming to capture reproducibility and consistency. Each session will take approximately an hour and volunteers will receive reimbursement upon completion of the study (€16,- in total). The size of the monetary reimbursement will be decided prior to the scanning procedures according to the scanning rates at the time of the experiment.

Both patient groups should be scanned according to fMRI protocols specific to epilepsy. Once the new scanning pipeline will be fully developed, the protocol can be applied to all types of hearing disabilities. The anonymous database created from the scans of healthy deaf volunteers will be shared via Open Science Framework (this is an option, which can be changed).

Importantly, to minimise the variability due to neuroplasticity changes, a list of requirements and limitations for participation will be made prior to contacting volunteers. To eliminate additional sources of variability and make the experiment more

reliable, these details should be communicated to the patient beforehand and documented during the acquisition. Patients should not drink coffee/tea on the day of the scan, get a full night's sleep and avoid medications. In terms of deaf epilepsy patient group scanning, the choice of anti-epilepsy medication should be documented and considered during the data analysis stages, since it might have an impact on structural and functional connectivity. Additionally, there are exclusion criteria due to the equipment utilised in the current research. That includes (1) metal in the body; (2) a pacemaker, neurostimulator or cochlear implants; (3) pregnancy; (4) skin diseases; (5) heart problems; (6) neurological/ psychiatric condition; (7) use of medications and drugs (except for oral contraceptives). Additional concerns might be developed during the literature review stages of this study and will be added to a clinical consent form, which patients read and sign prior to investigation.

Objective 1: The Scanning Protocol Development

The main aim for current protocol modification is switching classical epilepsy task-based fMRI protocol to accommodate for the inability to process audible stimuli.

There are currently available MRI machine models with a screen, that is visible to the patient while being positioned in the scanner. An example of that technology is a recent collaboration between Philips and Disney, which might still be in development [38]. This concept has been proposed for anxiety relief in paediatric patients and a more pleasant medical intervention experience overall. However, we believe that this technology can be adapted for deaf people's task-based MRI screening. As an example, the in-bore visibility can be used to visualise a pre-recorded video, either with text, images or gesticulating interpreter. Those would address the patient to perform tb-fMRI tasks. While in the scanner, the patient is usually given an emergency button. And we also need an impact from the patient during the scanning procedure, while assessing regional functionality. In the case of hearing patients, we can receive audible communication from their side during the scan time. The instructions are supplied through a headset and questions are asked directly by the clinicians performing a scan, while they are allocated in a scanning room since there is a microphone connecting clinicians in the scanning room and the patient, which is positioned in a scanner. The patient can answer the stated question since the scanning team has access to hear what's happening in a scanner. However, an alternative way to ensure two-way communication between a patient and clinicians is through emergency button reprogramming. Being able to adapt it to fit enough reactions to document the descriptive interaction of participants with tb-fMRI is the key. For example, pressing it once can mean yes, twice – no and three times – unclear. In case of emergencies, a patient would be required to hold the button.

The protocol should be developed with help from clinicians, sign language interpreters, MRI technicians and neurosurgeons. All the necessary safety precautions regarding potential visual epilepsy triggers should be studied and avoided in the alternative tb-fMRI method. This is just an idea, which should be better developed during the literature review stages in the first year of the proposed project.

Developing a new task-based functional magnetic resonance imaging (tb-fMRI) scanning protocol will start with a revision of the currently used tb-fMRI. Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS) protocol is proposed by the most recent guidelines and is implemented on 3 T MRI as the standard neuroimaging technique. It includes 2D coronal T2-weighted MRI, 3D FLAIR, and high-resolution 3D T1-weighted scans [1, 15, 17]. A higher signal-to-noise ratio can be achieved by using multiple head coils, as well as a shorter scanning time. Data acquisition is a trade-off between the efficiency of the scanning procedure and opportunities for analysis. A choice of analysis methods in a study often dictates scanning settings, however, when creating a publicly available dataset, we are favouring protocols that can produce data, that can be analysed with different methods and the least number of limitations. Additionally, this particular protocol should strongly avoid potential triggers (e.g. light flashes).

Objective 2: Data Collection and Analysis

It is important to ensure the safety of deaf epilepsy patients, as well as the ability to capture the necessary details, required to achieve the aim of the project: neuroplasticity investigation of the deaf community. Once the protocol is established, data collection can start in the DHV group, and then in the DEP. Once the data is collected, we will proceed to the data analysis stage. It can be conducted with various techniques and finding a suitable one is part of the research question. There are various existing packages in Python, and MATLAB, as well as independently created software, which can be exploited for data model estimation and denoising. Suggested literature for data pre-processing and analysis can be found in the references.

One of the proposed methods of white matter connection investigation is diffusion-weighted imaging (DWI). To be able to later perform the tract analysis, the scanning protocol should be advanced with preferred DWI sequences. To make use of DWI methods, like constrained spherical deconvolution, and to battle the issue of crossing fibers, we need to gather up DWI data with at least one non-zero b-value, 60 volumes and b-values in the range of 2,500 – 3,000 s/mm² [28, 39, 40]. We are aiming to research connectivity and expanding a standard scanning protocol with additional parameters will allow to probe microstructural organisation of biological tissues. The choice of scanning sequences will also dictate the possibilities of data denoising methods. For example, documenting the presence of the echo-planar imaging (EPI) distortions during the scanning

protocol creation will allow to battle the issue of EPI-related artefacts once we reach the data analysis stage. This will result in greater precision of the acquired data.

It would also be interesting to investigate volume fractions of dendrites and axons with neurite orientation dispersion and density imaging (NODDI) technique [42, 43]. This method requires similar scanning settings, like collecting multi-shell data, since it is one of the dMRI techniques. However, when compared to DWI, it allows for investigation of the individual contribution of the neural tissue components.

Objective 3: Connectome Analysis and Public Data Base Creation

Once the data is collected and structural differences are observed with the above-mentioned techniques, we may proceed to the next step, the main outcomes of which are expected to be:

1. Conducting the network connectivity analysis.
2. Comparing results in the group of deaf healthy volunteers to deaf epilepsy patients.
3. Collecting outcomes of this brain mapping method for evaluation.

An additional goal is a systematisation of the obtained data and preparing it to be publicly available. The Human Connectome Project (HCP) can be used as an inspiration for this step [44]. It is an online database, which demonstrates the first significant effort to gather and share human connectional anatomy and variation data with the general public. This project has been developed throughout 5 years of data collection and processing. Aiming to achieve the same level of quality and quantity within the 4 years PhD project would not be reasonable. That is why optimisation of the data collection method and choice of modern data analysis methods remains to be the first and crucial step of this research proposal. Structuring the dataset of deaf healthy volunteers and choosing a platform to make it publicly available would greatly benefit the research community.

The HCP data can be employed as a baseline when researching connectome in DHV and DEP groups. Since Diffusion Kurtosis Imaging (DKI) was implemented in HCP, it could be interesting to observe our acquired data with similar data estimation models. However, it is important to note that HCP was released in 2011, which made human connectome analysis possible, however many new techniques are developed and released every year. It is hard to predict which method will be used to obtain a third objective of the proposed research since it is one of the last stages of the planned project.

Project Timeline and Research Outcome

The collection of DHP data will be done within the first 2 years of the PhD project. Collection of DEP will start a year later and continue until the necessary number of patients can be involved in the study since the group of interest is not large. In case of difficulties, the sample size will be altered in order to perform an analysis of the acquired data within the four-year timeframe.

An extensive literature study will be conducted within the first year of the project, followed up by occasionally scheduled literature review periods. The outcome of the first literature should, firstly, guide the development of alternative tb-fMRI techniques, while being aware of potential epilepsy-related triggers and aware of brain functionality, being fired up in response to tb-fMRI tasks. Secondly, formulate a hypothesis on language area differences in deaf vs able-hearing individuals based on materials on neuroplasticity. Thirdly, conduct a relevant list of expected structural and functional changes due to the prolonged occurrence of epileptic seizures. And finally, investigate novel data analysis methods that could be utilised to meet the study outcomes. Based on this information, scanning protocols will be altered.

Backup approach

In case of the inability to implement suggested alterations to task-based fMRI language mapping protocol, a high-resolution resting state fMRI in combination with a method described by P. Branco will be implemented [26]. This method will be developed further if a backup plan is necessary. Currently, it is not adapted for sign language, which is the main communication way of the non-hearing community, so will have to be adjusted to accommodate for deaf epilepsy brain implications.

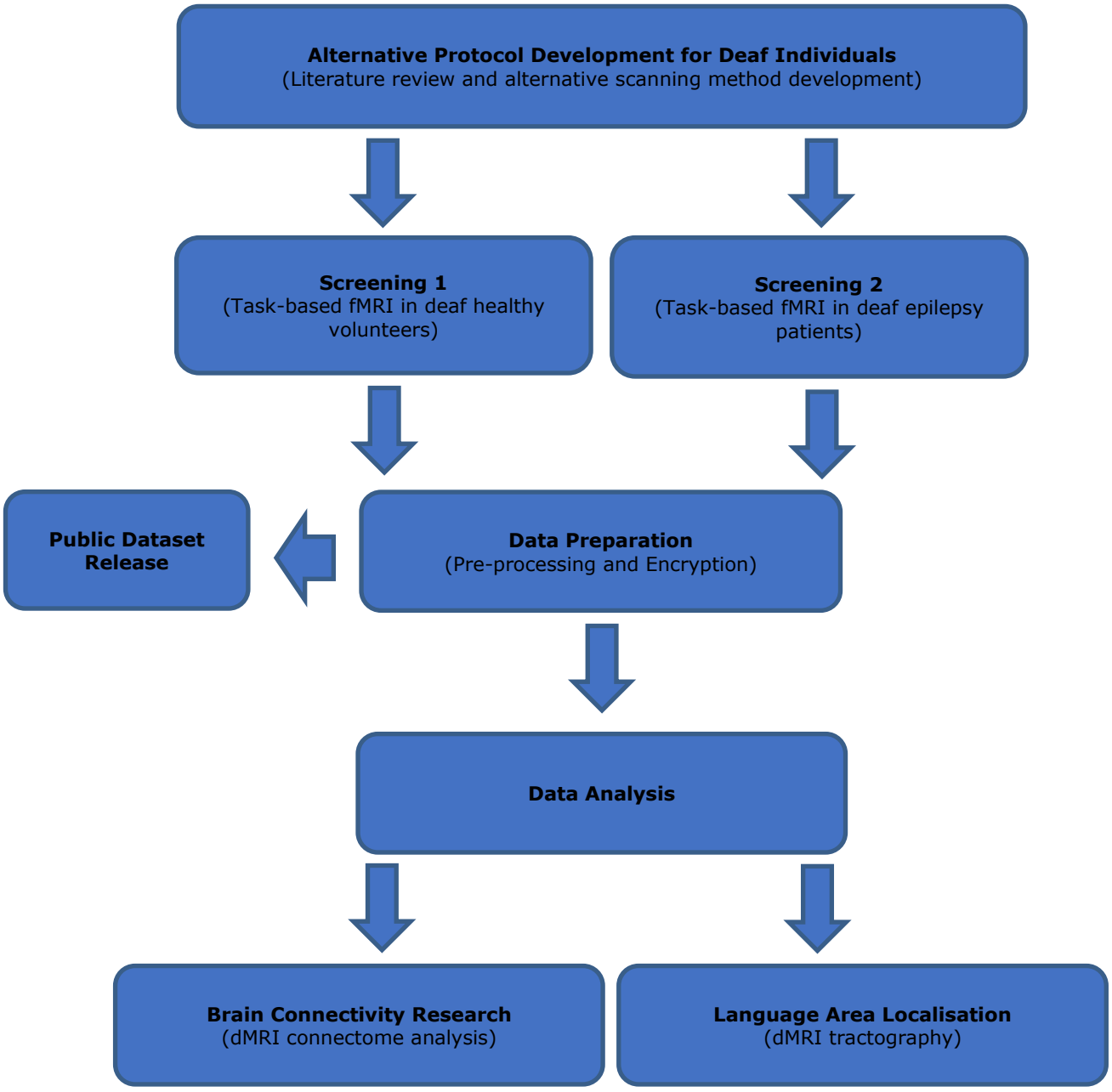

FIGURE 1. Study Design Planning

A schematic of the proposed research.
Upon modification of the current standard tb-fMRI protocol, deaf healthy volunteers will be scanned. Volunteers will be contacted and instructed about limitations related to the scanning procedure prior to the first scan. The scanning will be done twice within a period of two months. Then, data encryption (to protect volunteer privacy) and pre-processing will be implemented in preparation for a publicly available healthy deaf volunteer dataset release.
After the alterations according to safety considerations to the tb-fMRI protocol for deaf healthy volunteers, the experimental scanning of deaf epilepsy patients will begin.
In the meantime, connectome analysis will be performed with the use of diffusion MRI techniques in terms of the data analysis stage. The focus will be on the localisation of language centres (in healthy volunteers and epilepsy patients) and epileptogenic zone (epilepsy patients only). The comparison of language zone allocation will be done between the patients with the hopes to trace the repeatability of regional rearrangements in deaf people due to limitations in auditory stimuli processing.

B.2.3 Feasibility / Risk assessment

The proposed research is to be conducted at UMC Utrecht, which has the accessibility of 1,5 T, 3 T and 7 T MRI scanners. The main data-acquiring method of this project is fMRI. This method opposes minimal risk to participants, while sufficient precautions are considered. Strict MRI safety protocols will therefore be put into place to ensure participants' well-being. In studies involving vulnerable groups such as this one, it is important to ensure the absence of triggers (flashing lights during screening), close availability of an emergency button and options to pause the intervention.
Additionally, the volunteering group of interest is comparatively small. Due to these inconveniences, low participant retention is expected to be a risk for the completion of data collection. A monetary reward (€8,- euros per hour, to be paid upon completion of the study) will be provided to encourage participation from healthy deaf volunteers (the size of monetary reimbursement will be decided prior to the scanning procedures according to the scanning rates at the time of the experiment).

B.2.4 Scientific impact (a) and societal (b) impact

The proposed project aims to develop an alternative task-based functional magnetic resonance imaging (tb-fMRI) protocol for deaf people and deaf epilepsy patients, as well as to investigate neuroplasticity differences.

Firstly, by translating the currently available audible tb-fMRI instructions into visual interpretation, we make tb-fMRI available for deaf people. Developing an alternative tb-fMRI scanning protocol for deaf people, we simplify the pre-surgical brain mapping and, therefore, evaluation procedure. Configuring a new way to perform a pre-surgical assessment for deaf people would improve the accuracy guaranteed by the existing protocols, giving this group a higher chance of getting considered for surgery (since current evaluation for people with hearing disabilities is done with rs-fMRI, which is not sufficient for functional investigation). The protocol developed for deaf epilepsy patients can also later be adapted for other disabilities to make visual task-based fMRI a viable option for the bigger part of the population.

Secondly, acquiring a dataset of deaf healthy volunteers with a 7 T MRI machine will contribute to one of the first atlases with such a level of reliability thus far. The plan is to obtain data consistently (2 scans of each person within 2 months period) and with the smallest possible intra-subject variability (monitor caffeine intake, medication, sleep etc), so that inter-subject variability can be studied. Performing scans with 7 T MRI will aid higher resolution and lead to fewer limiting factors when choosing data analysis methods. Creating a publicly available high-resolution dataset of deaf people's brain scans will not only facilitate the research of connectivity in deaf epilepsy patients but it is also a valuable contribution towards the investigation of other neurocognitive pathologies in the deaf community. Making this dataset publicly available will popularise investigations of healthy anatomical and physiological configurations, but also pathologies and disabilities of the deaf community, which will help them to get better treatment. Our willingness to make the acquired dataset public is dictated by our strong belief in the concept of open science and that the scientific community (and eventually society as a whole) will greatly benefit from research achievements and discoveries, which are humbly shared with full transparency. Providing access will not only help researchers but also doctors and students to access data, pushing collective scientific achievements forward.

Thirdly, having access to such a dataset will allow us to study connectivity in deaf healthy volunteers, and deaf epilepsy patients and compare the results. Figuring out if the language area in deaf people differs from able-hearing individuals due to the auditory stimuli processing differences would impact the current scientific landscape. From this data also the structural and functional impact of prolonged epileptic seizures on brain connectivity will be studied. Understanding the differences in brain functionality is the first step to a deeper understanding of how to perform surgeries for epilepsy prevention since the amount of removed tissue highly depends on the ability to localise language areas and epileptogenic zone. Making use of a powerful 7 Tesla MRI scanner to acquire them, could provide a greater number of details and will be less dependent on technological limitations. Moreover, comparing the repeatability of functional brain region rearrangement in deaf people will help to understand connectomics and neuroplasticity more. The level of detail obtained by 7 T MRI will reveal previously unseen functional connections.

Finally, the data of good quality can allow us to revisit already existing proofs of functional connectivity, employing the newest diffusion-weighted imaging (DWI) advancements. Current sources and templates for brain tractography are mostly outdated. Having an opportunity to create an acquisition protocol and document necessary details is a big advantage when working with dMRI because this technique requires a strong hypothesis before the investigation. We will be using previously discovered connections as a template to perform the same evaluation on the data of better quality. That would result in a visual proof of the existing functional connectivity based on a task-based fMRI. That can also be reused for other research purposes that require fiber tractography.

One of the long-term aims of this project is the establishment of collaborations and data sharing. The deaf epilepsy patient group is comparatively small. This implies that reusing already acquired scans will be beneficial, as well as collaborations with research centres and hospitals that work on similar issues. This often comes with difficulties related to the standardisation of

the input format for further analysis. However, this can point out a previously unnoticed issue, which can be transformed into a research question. Optimisation of the multimodal previously acquired data for deaf epilepsy patients would allow revision of currently used protocols and improvement of procedures.

Overall, advancements in neuroimaging would lead to more patients being able to consider surgery as an option. It has been reported that some epilepsy cases, which respond to pharmacological treatment, would still benefit from getting surgery [50]. However, due to a high number of patients, it is mainly denied under the current conditions. Improvements in the epileptogenic zone and language centre localisation in combination with a better understanding of non-hearing patients' brain region functionality will imply higher certainty of surgical outcomes. Societally, it will result in patients' ability to gain control over the seizure occurrence, which reduces mortality and drastically improves the quality of life.

B.2.5 Ethical considerations

A publicly available dataset will be conducted from the healthy non-hearing volunteer scans. All the patient identity-related details will be removed, and only anonymised samples will be released. Data confidentiality will be ensured by data encryption during the collection and analysis stages. Only the authorised for this study researchers and clinicians will have access to personalised patient files. Data collection also requires informed consent, which will be collected through a phone interview and clinical screening forms. Even though fMRI is a non-invasive method associated with minimal risks, the scanning will be performed with extra care due to the alternative protocol being novel and experimental. Our primal responsibility will be ensuring patients' well-being and safety.

B.2.6 Literature/references

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