# IMAGINE-study (imaging study in epilepsy).
# Is there a neuronal correlate for cognitive impairment and response to antiepileptic drugs in children with frontal lobe epilepsy?

Published: 16-02-2009
Last updated: 05-05-2024

In this study we investigate correlations between cognitive impairment as well as response to AED treatment in children with FLE and brain microstructure, function and neuronal connectivity, by using DTI, task related fMRI, and resting state fMRI.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Seizures (incl subtypes) |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON32704

**Source**
ToetsingOnline

**Brief title**
IMAGINE-study (Imaging study in epilepsy)

### Condition

- Seizures (incl subtypes)

**Synonym**
Seizure/Epilepsy

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Epilepsie Centrum Kempenhaeghe
**Source(s) of monetary or material Support:** Kempenhaeghe

## Intervention

**Keyword:** Antiepileptic drugs, Cognition, Frontal lobe epilepsy, MRI

## Outcome measures

### Primary outcome

Abnormalities that are related to FLE, cognitive impairment and/or

refractoriness. Endpoints are the microstructural and functional integrity,

seizure history, IQ, and response to anti-epileptic drug

treatment.

### Secondary outcome

Patient-related and epilepsy-related factors responsible for cognitive

impairment and refractoriness.

# Study description

### Background summary

Frontal lobe epilepsy (FLE), i.e. epilepsy with a frontal epileptic focus, represents a substantial proportion of all partial epilepsies. The average age at onset of FLE is between 6 and 12 years. After the diagnosis FLE is made, the prognosis is still uncertain. Part of the children responds well to antiepileptic drug (AED) treatment, while others will become refractory and have frequent and disabling seizures. A second problem is that part of the children with FLE will suffer from cognitive impairment. The nature and severity of this impairment is highly variable, but it may seriously affect their development. Up to now, no clear patient or epilepsy-related factors responsible for refractoriness and/or cognitive decline have been identified, and structural MRI scans commonly reveal no abnormalities that may explain

this, even after years of ongoing seizures. Therefore, there are no markers to recognise this patient category. Hence, a diagnostic tool for the recognition of patients at risk for refractory epilepsy and cognitive impairment is needed to increase our understanding of the neuronal substrate and thus aetiology of refractoriness as well as cognitive impairment. Such a diagnostic tool may help clinical practice (define those that need more aggressive treatment strategies), and open new possibilities for pro-active therapy, including drug development and a more accurate determination of prognosis.
Magnetic resonance imaging (MRI) is a sensitive, safe, available and well-known technique to visualize brain structure. However, as mentioned, macrostructural brain abnormalities are commonly not found and are not expected in the early phase of epilepsy, hence in paediatric patients. Based on the type of cognitive impairments frequently observed in these children, functional networks in the frontal and/or temporal lobe are expected to be disrupted. Therefore we expect neuronal reorganisation especially in this early phase of the epilepsy, as this is the phase in which refractoriness and cognitive impairment develop.
Recently, more advanced MRI-techniques, including diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) became available. These techniques are capable of visualizing and assessing the level and integrity of functional networks. Such techniques may reveal the neuronal correlates of cognitive impairment and refractoriness on the level of microstructural and functional abnormalities. Such functional network changes have recently been observed by Vlooswijk et al (CODICE study) in adult frontal lobe epilepsy patients with cognitive impairment (Janssen & Vlooswijk, ISMRM 2008). This is in fact the long-term outcome of FLE and shows that once refractoriness and cognitive comorbidity have been developed, these functional network changes appear to be irreversible. The emergence of cognitive impairment and refractoriness are both observed early in the course of FLE thus in childhood. They develop slowly over the course of two or three years after the onset of the epilepsy, between the age of 8 to 12 years. Our study forms the third phase of investigations. First, Reijs & van Mil evaluated both the clinical course and the impact on cognitive development in children with frontal epilepsy, resulting in two PhD studies. These studies confirmed that a subset of patients develop refractoriness in a period of about two years after the onset of the epilepsy. Cognitive comorbidity developed in this same period, again in some children. Second, Janssen & Vlooswijk investigated whether neuronal correlates could be found in adults with FLE as this represents the long-term outcome of this process, again leading to two PhD studies. These studies demonstrated microstructural MRI changes and disruption of functional networks in those adults with FLE who suffer from cognitive impairment. Moreover, these changes seem to be irreversible as they are also seen in adult patients with low seizure frequency or those who are in remission. Therefore, any intervention must be at an early phase. Therfore, we now focus on the phase in which the neuronal changes develop to evaluate which changes are correlated with the resistance to treatment and which changes may explain the developmental arrest of cognitive functions. This can only be observed in children with FLE, i.e. in

the first years after the onset of the epilepsy

## Study objective

In this study we investigate correlations between cognitive impairment as well as response to AED treatment in children with FLE and brain microstructure, function and neuronal connectivity, by using DTI, task related fMRI, and resting state fMRI.

## Study design

Cohort study

## Study burden and risks

This study involves minors who are unable to give informed consent. Following the WHO guidelines, the *not unless* principle applies to granting permission for this study. The MRI-techniques and neuropsychological assessments that are applied in this study are non-invasive. The risks of a MRI-scan are negligible because it is a magnetic field, does not involve ionizing radiation and does not require contrast agents or anaesthetics. To minimize the burden, we will start with good education, including an information folder. Children can get used to the sound of the MRI-scan from a computer program. Children will be constantly guided by their parents and a specialized trial nurse. The scanning environment will be made as comfortable and cosy as possible. A Walt Disney movie will be displayed between the scanning sessions. In preparation, the children will be familiarized with the MRI system. The scanning time is 2 times 30 minutes with a half hour break in between (if necessary longer) and consists of individual programs with an average duration of 7 minutes. These sessions can be interrupted at any time. The neuropsychological assessment will take one hour in total. Recruitment of children in
the age of 8-12 years is essential as FLE is basically a disease of childhood and often disappears during adolescence (commonly with persistence of the cognitive impairments). Young adults are therefore not representative to unravel the development of neuronal correlates of refractoriness and cognitive comorbidity in FLE. The study of possible neuronal correlates of cognitive impairment and refractoriness in FLE requires the inclusion of an age-matched control group. There are three reasons for doing so. Firstly, all effects will be relative effects and not absolute effects that require a comparison with normal development to be able to understand. Secondly, apart from the secondary changes due to the seizures, brain development in children with FLE may as well differ from healthy subjects. Thirdly, MRI derived cerebral properties such as oxygenation changes due to brain activation and diffusion properties of white matter depends on age, and changes most strongly in the age category that makes up our study population. The imaging of the normally developing brain provides a necessary baseline for comparisons, both with FLE and FLE complicated by

cognitive impairment or refractoriness. To minimize the burden in the control group, we will perform the neuropsychological assessment and scanning during their holiday period and on the same day. Moreover, we will apply short scan protocols to minimize the magnet time of all the children.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

## Inclusion criteria

Inclusion criteria for the healthy adult group for the calibration study:
1. Adults aged 18 years or older
2. Normal intelligence;Inclusion criteria for children with FLE:
1. Age of 8 to12 years
2. Clinical and electroencephalographic evidence of seizures originating from the frontal lobe.

When EEG is not informative, the recording of more than one seizure with clinical evidence of seizures originating from the frontal lobe is required to make the diagnosis (Provini et al (1)).
3. Non-symptomatic epilepsy;Inclusion criteria for healthy control children:
1. Age of 8 to 12 years
2. Normal intelligence/following regular schools

## Exclusion criteria

Exclusion criteria for the healthy adult group for the calibration study:
1. Medical history of head trauma or other diseases/ causes that may underlie cognitive impairment (i.e. psychiatric diseases)
2. Inability to speak/understand the Dutch language
3. Vision less than +4.5D or - 4.5D
4. Claustrophobia
5. Metal implants or other contraindication for MRI
5. The expressed wish not te be informed whenever structural abnormalities are found during imaging;Exclusion criteria for children with FLE:
1. Multiple seizure foci involving more than one lobe of the brain documented on previous EEG studies
2. Frontal lobe seizures thought to be a result of spread to the frontal lobes
3. MRI lesions on previous structural brain MRI- or CT-scans or symptomatic epilepsy (e.g. tumours, vascular abnormalities, congenital dysgenesia)
4. Full scale IQ<70 on the Wechsler Intelligence Scale for Children-Third Edition (Wechsler 1991).
5. Progressive neurological disorders
6. Other diseases/ causes that may underlie cognitive impairment (i.e. psychiatric diseases)
7. Inability to speak/understand the Dutch language)
8. Cognitive deterioration directly after starting with AED, or treatment with Topiramate or Phenobarbital
9. Vision less than +4.5D or - 4.5D
10. Claustrophobia
11. Metal implants or other contraindication for MRI
12. Parents not willing to provide informed consent;Exclusion criteria for the healthy control children:
1. Medical history of head trauma or other diseases/ causes that may underlie cognitive impairment (i.e. psychiatric diseases)
2. Inability to speak/understand the Dutch language
3. Vision less than +4.5D or - 4.5D
4. Claustrophobia
5. Metal implants or other contraindication for MRI
6. Parents not willing to provide informed consent
7. Parents who do not want to get informed whenever structural abnormalities are found during imaging

# Study design

## Design

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|---|---|
| Study type: | Observational non invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Basic science

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 24-04-2009 |
| Enrollment: | 90 |
| Type: | Actual |

# Ethics review

Approved WMO

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| Date: | 16-02-2009 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| CCMO | NL25516.068.08 |