

Local axonal architecture and spontaneous dynamic BOLD fluctuations in bottom-of-sulcus-dysplasia: a model of cryptogenic location related seizures

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Primary objective: The ultimate goal is to achieve a more sensitive method for detecting malformations of cortical development. This encompasses two steps: the development of the method and the assessment of the sensitivity and specificity of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Observational non invasive

Summary

ID

NL-OMON35078

Source

ToetsingOnline

Brief title

LADYS study

Condition

- Structural brain disorders

Synonym

brain lesion, malformation of cortical development

Research involving

Human

Sponsors and support

Primary sponsor: Epilepsiecentrum Kempenhaeghe

Source(s) of monetary or material Support: Epilepsie Fonds

Intervention

Keyword: connectivity, epilepsy, focal cortical dysplasia, MRI

Outcome measures

Primary outcome

For DTI the quantitative outcome parameters will be the local apparent diffusion coefficient (ADC), fractional anisotropy (FA), and tract volume and tract FA values seeded in the white matter region close to the BOSD. These parameters will be obtained in the region close to the BOSD and the corresponding contralateral (normal) regions.

For rs-fMRI the correlation coefficient will be determined between the rs-fMRI time course signal from a region in the BOSD and all voxels in the rest of the brain. The resulting map will be compared with the same analysis seeded to the contralateral region. Besides the time courses, also the spectrum (Fourier transformed signal) of the time courses will be analyzed. For this the amplitudes of the spectral components in the high (> 80 mHz) and low (<80 mHz) frequency ranges will be compared between the BOSD region and the contralateral region.

Secondary outcome

Normal volunteers will be scanned twice to assess the inter-scan variability of the connectivity parameters.

Study description

Background summary

Epilepsy is one of the common neurologic syndromes with a lifetime incidence of 2-4% and about 50% of these patients suffer from partial seizures. Neuroimaging is used to determine the origin of these seizures. However, in a large proportion of these patients with partial seizures, MRI shows no abnormalities. Even with state-of-the-art imaging techniques many localization-related seizures remain cryptogenic. It is assumed that the majority of these patients have a small cortical dysplasia. Detecting these lesions is of clinical importance in patients with intractable epilepsy, because resection of these focal lesions may be the only viable therapeutic option and there is an excellent prognosis for seizure control following focal resection (Urbach 2002).

Different imaging strategies have been implemented to increase the sensitivity for the detection of such small malformations. Advances in MRI technology have certainly improved image quality and consequently increased the detection rate. Despite these improvements, a large proportion of studies remain negative. Post-processing techniques have also been applied to the imaging data to improve the conspicuity and detection rate of small lesions.

These techniques employ voxel-based morphometry and parametric mapping of cortical thickness and gray-white matter transition to increase the sensitivity of MRI for the detection of malformations of cortical development. However, these studies have not shown a consistently improved sensitivity compared with visual image reading.

With visual assessment as gold standard the sensitivity of these techniques is between 78 and 90% with a reported specificity between 50 and 100% (Antel 2002, Huppertz 2005, Bonhilha 2006, Colliot 2006).

Another approach is to use novel imaging techniques that rely on different intrinsic contrast mechanisms and may show previously unrevealed lesions. There are a number of such novel MRI contrasts that have been shown to be more sensitive for cerebral abnormalities than conventional MRI.

Two of these techniques are resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI).

DTI (Pierpaoli 1996 a&b, Helpert 1995) show reversible changes in active regions during status epilepticus (e.g. Szabo 2005, Farina 2004, Hufnagel 2003, Diehl 1999).

Although these reversible changes on MRI are most prominent in patients after a status epilepticus and prolonged seizures and are rarely seen after a normal seizure (Cianfoni ASNR 2009), this does have implications for patient selection. Patients should be seizure free for at least a few days and they should not have suffered from prolonged seizures or a status in the last two months. However, the brain is a dynamic organ and when dealing with connectivity there is no clear distinction between functional and structural changes. In part, this distinction is not relevant as long as these techniques increase the sensitivity for the detection of epileptogenic lesions.

DTI can also be used to show aberrant fibre connections in cerebral malformations (Lee 2005). In post-traumatic brain injury regional DWI and DTI parameters are more disturbed in patients with epilepsy as compared to those without epilepsy (Gupta 2005). As such DTI provides data on the structural connectivity and micro-structural integrity of the brain.

Rs-fMRI provides information about the (unconditional) synchronicity of spontaneous temporal blood signal fluctuations between different brain regions based on the blood oxygen level dependent (BOLD) effect and can be used to map the functional connectivity as opposed to the structural (i.e. axonal) connectivity as assessed by DTI.

There is however a fundamental problem with the application of these technique for the detection of small malformations of cortical development. That is the lack of a gold standard. Visual assessment of MRI scans is mainly based on pattern recognition and if a cortical region has deviant morphological features as compared to the surrounding cortex it is presumed abnormal. This technique was proven to be specific, because a high correlation was found between abnormalities on conventional MRI and the histopathology of the resected lesions. Such pattern recognition is not yet possible in connectivity studies because it is not clear yet which features distinguish normal from abnormal cortex.

To this tackle this issue, we propose to use a very specific and well-defined type of cortical dysplasia as a model to study small cortical malformations of structural and functional connectivity.

A recently described archetype of focal cortical dysplasia may serve as such a model for small cortical lesions. In the 2005 revision of the Barkovich classification (Barkovich 2005), a new type of MCD was proposed; bottom-of-sulcus dysplasia (BOSD) and it is classified in the group of malformations due to abnormal proliferation, FCD with balloon cells. The lesion may be difficult to detect on MRI and, even in expert centres*, is often missed by experts on initial inspection of images. The imaging characteristics are those of FCD of the Taylor type. However, the typical location of the dysplasia at the bottom of a sulcus is infrequently seen in what we would normally call typical FCD of the Taylor type. The pathological features of the resection specimens are identical to those of any FCD. In FCD of Taylor type, the dysplasia that probably overlaps with the BOSD, cortical laminar disorganization, giant, ectopic and dysmorphic neurons is found. Gliosis is also a prominent feature (Basto 1999). Hypomyelinated white matter and radially orientated balloon cells are also reported (Urbach 2002). BOSD poses a diagnostic challenge because of the small size and the location of the lesion. The major problem with BOSD is that they can be subtle and easily missed on initial examination of images. Diagnosis is greatly aided by having images with excellent signal-to-noise ratio so that the blurring of the grey-to-white-matter junction at the bottom of the sulcus can be properly appreciated as well as the increased signal intensity of the cortex and underlying white matter on T2-weighted images.

Furthermore, the post-surgical outcome appears to be excellent after complete

resection as reported (Urbach 2002). It appears that the disturbance is very focal and the surrounding brain is not affected. With advancing imaging techniques the detection rate of such small lesions is improved and a recent publication showed that 68% of all FCDs were located in the depth of a sulcus (Besson 2008). There is a continuum of increasing abnormalities in the histology of cortical dysplasia from Palmini type IA to type IIB, and because many of these lesions are in the ictal onset zone we postulate that the MR image and connectivity characteristics also will show a continuum of increasing abnormalities (Palmini 2004). Therefore, we propose to use BOSD, a Palmini type IIB lesion, as a model for the up to now undetected cortical malformations. BOSD is small, with only focal histological abnormalities, also illustrated by the good outcome after focal resection of these apparently highly epileptogenic lesions. Once this model type of dysplasia is fully characterized in terms of rs-fMRI and DTI measures, more, thus far undetected, small lesions may become detectable.

- Antel et al. Computational models of MRI characteristics of focal cortical dysplasia improve lesion detection. *Neuroimage* (2002) vol. 17 (4) pp. 1755-60
- Barkovich AJ, Kuzniecky RI, Jackson GD, et al. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;65:1873-1887
- Bastos AC, Comeau RM, Andermann F, et al. Diagnosis of subtle focal dysplastic lesions: curvilinear reformatting from three-dimensional magnetic resonance imaging. *Ann Neurol* 1999;46:88-94
- Besson P, Andermann F, Dubeau F, et al. Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus. *Brain* 2008;131:3246-3255
- Colliot et al. Individual voxel-based analysis of gray matter in focal cortical dysplasia. *Neuroimage* (2006) vol. 29 (1) pp. 162-71
- Diehl B, Najm I, Ruggieri P, et al. Perictal diffusion-weighted imaging in a case of lesional epilepsy. *Epilepsia*. 1999 Nov;40(11):1667-71.
- Bonilha et al. Voxel-based morphometry reveals excess gray matter concentration in patients with focal cortical dysplasia. *Epilepsia* (2006) vol. 47 (5) pp. 908-15
- Cianfoni, A. et al. Seizure-Induced Reversible or Partially Reversible Brain MR Imaging Signal Abnormalities: Multicentric Experience on 19 Consecutive Patients with Hippocampal Sclerosis: Comparison MR Imaging, FDG-PET and Pathology . *ASNR* 2009 p9.
- Farina L, Bergqvist C, Zimmerman RA, et al. Acute diffusion abnormalities in the hippocampus of children with new-onset seizures: the development of mesial temporal sclerosis. *Neuroradiology*. 2004 Apr;46(4):251-7.
- Gupta RK, Saksena S, Agarwal A, et al. Diffusion tensor imaging in late posttraumatic epilepsy. *Epilepsia*. 2005 Sep;46(9):1465-71
- Helpert JA, Huang N. Diffusion-weighted imaging in epilepsy. *Magn Reson Imaging*. 1995;13(8):1227-31
- Hufnagel A, Weber J, Marks S, et al. Brain diffusion after single seizures. *Epilepsia*. 2003 Jan;44(1):54-63.

- Huppertz et al. Enhanced visualization of blurred gray-white matter junctions in focal cortical dysplasia by voxel-based 3D MRI analysis. *Epilepsy Res* (2005) vol. 67 (1-2) pp. 35-50
- Lee SK, Kim DI, Kim J, et al. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. *Radiographics*. 2005 Jan-Feb;25(1):53-65; discussion 6-8.
- Palmini et al. Terminology and classification of the cortical dysplasias. *Neurology* (2004) vol. 62 (6 Suppl 3) pp. S2-8
- Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance Medicine* 1996; 36:893-906
- Pierpaoli C, Jezzard P, Basser PJ, et al. Diffusion tensor MR imaging of the human brain. *Radiology* 1996; 201:637-648
- Szabo K, Poepel A, Pohlmann-Eden B, et al. Diffusion-weighted and perfusion MRI demonstrates parenchymal changes in complex partial status epilepticus. *Brain*. 2005 Jun;128(Pt 6):1369-76.
- Urbach H, Scheffler B, Heinrichsmeier T, et al. Focal cortical dysplasia of Taylor's balloon cell type: a clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. *Epilepsia*; 2002. p. 33-40.

Study objective

Primary objective: The ultimate goal is to achieve a more sensitive method for detecting malformations of cortical development. This encompasses two steps: the development of the method and the assessment of the sensitivity and specificity of the method. The aim of the current project is to achieve a characterization of the functional and structural connectivity of a specific type of focal cortical dysplasia that can serve as a model for more subtle dysplasias. When successful, the second step, the assessment of the new technique on patient with location-related cryptogenic seizures will be the subject of a subsequent separate study.

Study design

Using high-resolution DTI the local architecture of the normal and abnormal cortex is imaged. During both image data acquisition as well as post-processing the variable and complex anatomy is taken into account. Based on the DTI analysis the different sub-regions of the abnormal gyrus will be segmented based on the local tractographic topology. This is only possible with *high angular resolution diffusion imaging* (HARDI), which encompasses 54-128 independent diffusion measurement directions.

The rs-fMRI will be used to characterize the spontaneous fluctuations of the BOLD response in and around the BOSD and compare these results with the controls. Spectral analysis will be applied in the assessment of rs-fMRI with spectral density in the high (>80 mHz) and low frequency (<80 mHz) range will

be used as outcome variable.

Addendum 7 and 14

For DTI the quantitative outcome parameters will be the local Apparent Diffusion Coefficient (ADC), Fractional Anisotropy (FA), and tract volume and tract FA values seeded in the white matter region close to the BOSD. These parameters will be obtained in the region close to the BOSD and the corresponding contralateral (normal) regions.

For rs-fMRI the correlation coefficient will be determined between the rs-fMRI time course signal from a region in the BOSD and all voxels in the rest of the brain. The resulting map will be compared with the same analysis seeded to the contralateral region. Besides the time courses, also the spectrum (Fourier transformed signal) of the time courses will be analyzed. For this the amplitudes of the spectral components in the high (> 80 mHz) and low (< 80 mHz) frequency ranges will be compared between the BOSD region and the contralateral region.

DTI and rs-fMRI measures will be compared.

Study burden and risks

The MRI-techniques and questionnaire that are used in this study are non-invasive. Therefore, the risks of participating in the study is minimal. 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 nor anaesthetics.

Theoretically, it is possible that structural abnormalities will be found during MRI in the healthy control group. Therefore, we will include only subject who want to be informed whenever structural abnormalities are found during imaging. All patients had a previous brain MRI which showed a focal cortical dysplasia.

Benefit: There is no benefit for the patients or volunteers in this study, however the potential benefit for epilepsy patients with a negative conventional MRI is substantial; if a lesion is detected and a surgical approach is possible, these patients may become seizure free.

Contacts

Public

Epilepsiecentrum Kempenhaeghe

Sterkselseweg 65

5591 VE Heeze

NL

Scientific

Epilepsiecentrum Kempenhaeghe

Sterkselseweg 65
5591 VE Heeze
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Patients:

Legally capable adults with and the diagnosis of localization-related seizures and a BOSD on a state-of-the art 3 Tesla MRI. Based on the seizure semiology and EEG the BOSD must be most likely epileptogenic focus. In our files we have over 50 patients who fulfil the inclusion criteria for this study.

Normal volunteers:

Legally capable adult volunteers without a serious medical problem and no medical history of head trauma or other neurological or psychiatric diseases.

Exclusion criteria

Contra indications for MRI

For the normal volunteers:

medical history of head trauma or other neurological or psychiatric disease

the expressed wish not to be informed whenever structural abnormalities are found during imaging

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2011
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO	
Date:	19-07-2010
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	NL31508.068.10
Other	www.trialregister.nl