

Functional connectivity and neuronal networks in brain tumor patients with epilepsy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational non invasive

Summary

ID

NL-OMON37154

Source

ToetsingOnline

Brief title

Brain networks and epilepsy

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Seizures (incl subtypes)

Synonym

brain tumor, Seizures

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

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

Intervention

Keyword: Brain Neoplasms, Epilepsy, Neural Networks (functional)

Outcome measures

Primary outcome

- MEG-measures:

clustercoefficient

padlength

synchronisation likelihood

- epilepsy diary (frequency and severity) and epilepsy burden

Language-study

The main study parameters are an extensive language task, a naming task and a language performance questionnaire assessing functional outcome in patients who received resective brain surgery after intraoperative language mapping. The language task will measure language performance in various domains, e.g. speaking, listening, reading and writing, whereas the questionnaire will obtain information on how patients perceive their own language performance. The naming task will measure performance pre and post operatively.

Secondary outcome

cognition

Language-study

The secondary study parameters are the neuropsychological tests obtained pre-

and postoperatively by a neuropsychologist.

Study description

Background summary

Approximately 80% of patients with low-grade and 45% of patients with high-grade glioma suffer from epileptic seizures. Among these patients, there is a large inter- and intra-individual variability in seizure severity and frequency, the cause of which has not been elucidated in earlier research.

In order to understand more of the complex mechanisms involved in epileptic seizures in brain tumor patients, the neural network architecture of the brain can be investigated. It is widely acknowledged that the paroxysmal phenomenon of epilepsy is related to hyperexcitation of neurons, leading to changes in the synchronization of large neuronal networks during the seizure. Spatial features of neural networks determine to what extent the network facilitates such synchronization. Moreover, networks with more long distance connections, a so-called **random** configuration, are thought to have a lower threshold for synchronization. A possibly influential feature of functional networks is the small-world characteristic, referring to the high degree of interconnectedness between single units in a network.

Previous studies using computational models have suggested a correlation between changes in network structure and epilepsy. Netoff et al. simulated a network model of excitatory neurons in hippocampal slices and changed the parameters of the network (e.g. proportion of local versus long-distance connections). They found that the start of the bursting phase corresponds with a more random architecture. Percha et al. showed a potential mechanism underlying seizure generation, as properties of phase synchronisation changed radically depending on the structure of the network, which may play an important role in the emergence of seizures. Dyhrfeld-Johnsen et al. recently demonstrated by means of a computational model that in the rat dentate gyrus neuronal loss, similar to the loss observed in hippocampal sclerosis, is accompanied by a more random network configuration.

On the basis of these studies, it is suggested that the architecture of the underlying neuronal network determines whether a patient is more or less prone for the development of seizures. The more random a network, the more susceptible it may be to whole system synchronization. In contrast, networks with a less random and more small-world configuration, while still having a low threshold for synchronization, are expected to be more stable [16, 17]. We think it highly interesting to investigate whether network characteristics and epilepsy features are correlated in glioma patients.

In our previous research, low-grade glioma (LGG) patients displayed cognitive deficits. These deficits were strongly related to epilepsy burden (assessed by the Engel Scale), and the use of antiepileptic drugs (AEDs). We have recently shown that a correlation exists between cognitive functioning and functional connectivity in LGG patients. The relation between (1) network structure, (2) epilepsy, and (3) cognition remains to be clarified.

Language-study:

Surgical treatment of brain tumours has been advocated by numerous authors in the past decade (Duffau, 2008). The goal is to obtain maximum resection of the tumour, as survival is improved with this (Duffau, 2009, Sanai, 2008). Although survival is improved, there is a chance that there is an occurrence of functional loss after surgical removal of the tumour. In order to prevent functional loss, intraoperative function mapping is applied during awake surgery.

One of the important functions that can be affected during resective brain surgery is language. Intraoperative language mapping is considered the gold standard to identify cortical and subcortical language structures. A picture naming task is administered, while the neurosurgeon applies direct cortical stimulation on various (sub)cortical sites. If a naming error occurs during stimulation this indicates that the stimulated (sub)cortical site is essential for language function. This site will then be preserved during tumour resection, to minimize language deterioration postoperatively. Currently, picture naming and counting are the most commonly used tasks during intraoperative language mapping to identify language sites (Duffau, 2008, Sanai, 2008, Ilmberger, 2008).

Most studies use a picture naming task to test the language abilities in the postoperative period. Research shows that in the immediate postoperative period there is a decrease in language performance on this task compared to the performance on the task before surgery. Three months after tumour resection most studies indicate that patients returned to their baseline score or even had an improved score compared to score before surgery. These results suggest that there is no longer a reduced language performance in these patients. However, in a subset of patients language performance is reduced. As the picture naming task is relatively simple, it is presumed that the task may not be sufficient enough to detect subtle but important language deficits.

Therefore, an extensive language task is needed to detect language deficits. Only a few studies have used an extensive language task to examine language performance in patients treated with resective surgery. One study investigated writing, reading, repeating, naming and counting, and showed that six months after surgery a subset of patients had a persisting language deficit (Sanai, 2008). Two studies used parts of the AAT to investigate language performance. One study found that 3 months after surgery 42 patients out of 128 patients who had no disturbance pre-operatively showed a language disturbance (Ilmberger, 2008). It was found in another study that three months after surgery 15 out of 29 patients had a reduction in spontaneous speech and mean length of utterances. (Visch-Brink, 2010) Another study found that although positive

language sites were preserved, some patients were unable to write after removal of the tumour (Duffau, 2009).

The present study will therefore examine language performance of the treated patients with an extensive language test to characterize language disorders resulting from resective brain surgery. In addition, a language related questionnaire will also be obtained. This will provide insight in how patients experience their own language performance.

Study objective

The current study aims to investigate whether neural network characteristics of the brain can predict the frequency and severity of epileptic seizures in brain tumor patients. Our secondary objective is to determine the correlation between seizures, network architecture and cognition in this patient group.

Language-study:

The primary aim of the research is to establish the characteristics of language disorders in patients that have had resective surgery of a tumour in the dominant hemisphere.

Study design

Longitudinal case-controlled observational study

Language-study:

This is a prospective controlled study and will be conducted at the VU University Medical Centre in Amsterdam.

Brain tumour patients who received intraoperative language mapping and resective brain surgery in their dominant hemisphere will be asked to participate in the present study. In order to assess their language outcome after surgery an extensive language test and a language related questionnaire will be conducted. The inclusion of patients and data obtainment will start in January 2011 and will end in April 2011.

We will investigate whether language performance is affected in patients treated with resective brain surgery, despite the preservation of eloquent language areas indicated with intraoperative language mapping. An extensive language test will be used to objectively measure the language performance in this patient group. A naming task will be included as well, to compare pre and post operative data. In addition, a language related questionnaire will be utilized to investigate how patients perceive their language performance.

Study burden and risks

For patients, the burden associated with participation consists of a number of visits to the outpatients* clinic for MEG measurements and neuropsychological screening. Furthermore, they will be asked to keep a diary regarding the

frequency and severity of epileptic seizures during the course of their disease, which is routine practice in patients with epilepsy. For controls, the burden of participation consists of a one time only visit to the outpatients* clinic for MEG registration. No health-related risks are involved in this study. In our view, the burden associated with participation is proportionate to the potential value of the research for (glioma) patients suffering from epilepsy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Inclusion criteria for glioma patients:

(1) adult (> 18 years)

(2) epilepsy (at least one epileptic seizure)

- (3) histopathologically confirmed glioma or meningioma according to the WHO
- (4) written informed consent; Inclusion criteria for healthy controls
- (1) adult (> 18 years)
- (2) written informed consent; Inclusion criteria for language side-study (amendment):
- (1) received intraoperative language mapping
- (2) received resective brain surgery in the dominant hemisphere
- (3) Dutch is native language

Exclusion criteria

Exclusion criteria for glioma patients:

- (1) psychiatric disease or symptoms
- (2) insufficient mastery of the Dutch language
- (3) inability to communicate adequately; Exclusion criteria for healthy controls:
- (1) use of centrally acting drugs (including analgetics)
- (2) psychiatric disease or symptoms
- (3) disorders of the central nervous system
- (4) insufficient mastery of the Dutch language

Study design

Design

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:	Recruitment stopped
Start date (anticipated):	18-06-2008
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO

Date: 04-06-2008

Application type: First submission

Review commission: METC Amsterdam UMC

Approved WMO

Date: 01-02-2011

Application type: Amendment

Review commission: METC Amsterdam UMC

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	NL22019.029.08