

Cornelis Jan Stam

Department of Clinical Neurophysiology, VU University
Medical Center, Amsterdam, The Netherlands

Summary

The clinical neurophysiology of epilepsy has recently witnessed several interesting new developments such as the discovery of high frequency oscillations, the use of MEG virtual sensors, and graph theoretical approaches to epileptic brain networks. This short review introduces the reader into some of the basic concepts of modern network theory and their application to brain networks. Epilepsy is shown to be characterized by two changes in network organization: (i) a shift from global to local connectivity (hyperregular networks), in the interictal as well as the ictal state; (ii) the presence of local pathological hubs in the vicinity of the actual epileptic focus. The pathological hub is suggested to be the gatekeeper between local and global brain networks, and could be an interesting target for improved diagnosis and selection of surgical targets in epilepsy surgery. Finally, network concepts may be helpful as biomarkers of chronic global brain damage and cognitive dysfunction in epilepsy.

Epileptologie 2016; 33: 38 – 43

Key words: Networks, hubs, high frequency oscillations, virtual sensors, graph theory

Epilepsie: Was wir von modernen Netzwerktheorien lernen können

Die klinische Neurophysiologie der Epilepsie hat in jüngster Zeit einige interessante neue Entwicklungen erlebt, zum Beispiel die Entdeckung von Hochfrequenzoszillationen, die Anwendung virtueller MEG-Sensoren und die graphentheoretische Annäherung an epileptische Hirnnetzwerke. Diese kurze Übersicht bietet eine Einführung in einige grundlegende Konzepte der modernen Netzwerktheorie und ihre Anwendung bei Hirnnetzwerken. Kennzeichnend für die Epilepsie sind zwei Änderungen der Netzwerkorganisation: (i) eine Verschiebung von der globalen hin zur lokalen Konnektivität (hyperreguläre Netzwerke) sowohl in der iktalen als auch in der interiktalen Phase; (ii) das Vorliegen lokaler pathologischer Schaltstellen in der Nähe des eigentlichen epileptischen Herds. Die pathologi-

sche Schaltstelle fungiert vermutlich als Weichensteller zwischen lokalen und globalen Hirnnetzwerken und könnte mit Blick auf eine verbesserte Diagnostik und die Auswahl der Zielstrukturen für epilepsiechirurgische Massnahmen interessant sein. Schliesslich können Netzwerkkonzepte auch als Biomarker für chronische Hirnschäden und kognitive Dysfunktionen bei Epilepsie dienen.

Schlüsselwörter: Netzwerke, Schaltstellen, Hochfrequenzoszillationen, virtuelle Sensoren, Graphentheorie

Epilepsie : que pouvons-nous apprendre des théories modernes des réseaux ?

La neurophysiologie clinique de l'épilepsie a connu récemment plusieurs nouvelles évolutions intéressantes, telles que la découverte des oscillations à haute fréquence, l'utilisation de capteurs virtuels de MEG, et les approches des réseaux cérébraux de l'épilepsie basées sur la théorie des graphes. Ce petit passage en revue présente au lecteur certains des concepts de base de la théorie moderne des réseaux et leur application aux réseaux du cerveau. L'épilepsie se veut caractérisée par deux changements dans l'organisation du réseau : (i) un passage de la connectivité globale à une connectivité locale (réseaux hyperréguliers) dans l'état interictal et dans l'état ictal ; (ii) la présence de centres pathologiques locaux à proximité du véritable foyer épileptique. Le centre pathologique semble être le garde-barrière entre les réseaux locaux et globaux du cerveau et pourrait constituer une cible intéressante pour un diagnostic amélioré et une sélection de cibles opérables en chirurgie épileptique. Enfin, les concepts de réseaux peuvent être utiles en tant que biomarqueurs de lésions cérébrales globales chroniques et de dysfonctionnement cognitif dans le cadre d'une épilepsie.

Mots-clés : Réseaux, centres, oscillations à haute fréquence, capteurs virtuels, théorie des graphes

*Based upon a Dutch text for the Biomed course on epilepsy and sleep disturbances.

Introduction

Use of neurophysiological techniques in epilepsy has recently been supplemented with other techniques such as genetic investigations and advanced imaging with PET, structural and functional MRI. The field of neurophysiology itself has also witnessed a number of interesting new developments that increase our understanding of the pathophysiology, and also open up new perspectives to improve diagnosis. Three examples of such developments are (i) the discovery of “high frequency oscillations”, in particular “fast spindles” (oscillations of 250 - 500 Hz) that are increasingly considered to be specific markers of the epileptic focus [1]; (ii) use of MEG and so-called virtual sensors to detect epileptiform activity in deep brain structures such as the hippocampus [2]; (iii) the idea that epilepsy can be viewed as a network disorder of the brain, where local and global changes in structural and functional networks all play a role in the spreading of seizure activity through the brain and the development of cognitive disturbances [3]. The aim of this contribution is to provide a better understanding in particular of the last development: brain network concepts in epilepsy. As will become clear the other two new developments will also be addressed briefly. The first question however is what is so special about brain networks, and why would this be relevant for epilepsy?

Brain networks

Ramon Y. Cajal was probably the first investigator who showed convincingly that our brain is a complex network of interconnected neurons. The human brain consists of approximately 10^{10} neurons, and each neuron has about 10^4 connections with other neurons. This complex network is ordered hierarchically, from individual neurons, micro- and macrocolumns in the cortex, all the way up to Brodmann areas, brain lobes and hemispheres. Neurological thinking assumes that the hierarchical organization and topological differentiation are closely related to function: we have “regions” for sensory and motor function, hearing, vision, language and so on. In this approach the network character of the brain is not yet fully clear, with the exception of a number of disconnection syndromes. Neurological diagnosis was and still is, to an important extent, based upon localization supported by neurological and ancillary (usually imaging-based) investigations. This is now starting to change due to new insights from the theory of complex networks [4].

Modern network theory is a multidisciplinary field of research with contributions from mathematics, physics, sociology and biology, among others. Around the turn of the century there have been a few important developments such as the discovery of “small-world” and “scale-free” networks [5, 6]. In a small-world net-

work there is an optimal balance between local communication and global integration of information processing [7]. Scale-free networks are characterized by so-called “hubs”: network nodes with many more connections than other network nodes, and a central role in efficient communication in the network. It has now become clear that the central nervous system in animals as well as humans displays the typical characteristics of both small-world as well as scale-free networks. This is equally true for structural as well as functional networks. This optimal organization of brain networks has a strong genetic basis, and is associated with cognitive function. By now various large-scale research projects have started to obtain a complete description of the human “connectome” (a complete map of the human brain network, analogous to that of the genome). There is now increasing evidence that changes in the human connectome may play a crucial role in various neurological and psychiatric disorders such as Alzheimer’s and Parkinson’s disease, multiple sclerosis, traumatic brain injury and schizophrenia. It is remarkable that the nature of the network changes in all these different disorders shows some striking resemblances. In all of these disorders there is evidence of involvement of the most central “hub” areas of the brain, in particular the so-called default mode network [8]. In this context it is interesting to know which network changes have been found in epilepsy and how they fit into this pattern. In addition, it is important to understand what could be the clinical relevance of these findings.

Ictal network changes

The idea that network organization might affect the flow of information on networks was already suggested in the pioneer studies of Watts and Strogatz and Barabasi and Albert [5, 6]. Only a few years later model studies with simulated neural networks suggested that abnormal network organization could lower the threshold for the spreading of seizure activity through a neural network [9]. One study showed that hub nodes might be of special importance in facilitating seizure spread [10].

The relevance of network organization for epileptic seizures in humans was first demonstrated in 2007 [11]. In this study in patients who were implanted with intracerebral electrodes in the workup for epilepsy surgery, the organization of the network, derived from correlations between EEG signals of different brain regions, changed from a small-world network in the interictal state to an abnormally regular network during and shortly after the seizure. An epileptic seizure is apparently characterized by a rather outspoken, temporal change in organization of functional brain networks, in which the normal balance between local and global connectivity is lost. This pattern of a temporary “hyperregular” structure of functional brain networks during an epileptic seizure has now been confirmed in a

number of studies with intracranial recordings [12, 13]. This pattern can even be observed with routine scalp recorded EEG during absence seizures [14]. Ictal hyperregularity has been found in focal as well as generalized epilepsy. The question is whether network changes can already be detected before seizure onset, in the preictal state. Such interictal network changes could be interesting from the point of view of diagnosis, locus localization or, eventually, seizure prediction.

Interictal network changes

The first assumption was that the interictal network might have an abnormally random structure [11]. This hypothesis was based upon two considerations: (i) it was known from network theory that random networks have a lower threshold for spreading synchronous activity through the system; (ii) epilepsy is often a reflection of local or global damage to the brain, and such damage is often associated with a transition of the normal small-world organization (with an optimal balance between local and global connectivity) to a pathological random organization. Although some early studies appeared to give support for this apparently plausible hypothesis [15], it has become increasingly clear that the opposite hypothesis may actually be closer to the truth. In a study in an animal model of focal epilepsy it was shown that the interictal network was also abnormally regular (like the ictal network, but to a somewhat lesser extent. Connectivity was increased near the epileptic focus, and decreased globally over long distances [16]. This interictal hyperregularity has been found in patients with various neuroimaging techniques [17]. Notably, abnormalities have been observed not only in functional networks, based upon EEG and functional MRI, but also in structural brain networks using structural MRI (tractography; cortical thickness networks) [18]. A recent metaanalysis of studies on functional and structural brain networks in epilepsy confirmed that this pattern of increased local connectivity and decreased global connectivity is very likely [19]. This raises the question how epileptic seizures can spread in a brain network where global integration is actually decreased. To be able to understand this paradox it is necessary to reconsider the role of the previously mentioned “hub” areas [10].

A better understanding of the role of hubs in epilepsy has been obtained mainly from intracranial recordings in the workup for epilepsy surgery. In studies with electrode grids or depth electrodes it was noticed that there were often some electrodes that could be characterized as hubs, for instance because their activity was abnormally synchronized with the activity at other electrodes [20]. Outcome of epilepsy surgery was more favourable if the hub areas were included in the resection area and less favourable when they were not included [21, 22]. On the basis of this type of observa-

tions it was assumed that hubs might somehow be involved in the spreading of seizure activity.

The focus in the network (HFOs and hubs)

This raises the question what the relationship between these pathological hubs on the one hand, and the actual epileptic focus on the other hand might be. In the mean time it has become clear that the epileptic focus, or more strictly the irritative zone, constitutes an area that is responsible for (i) the classic epileptiform abnormalities (spikes, spike wave complexes); but also (ii) extremely fast, abnormal oscillations in epileptogenic tissue [1]. These fast oscillations are referred to as “high frequency oscillations” or HFOs. In particular the fast variant, the “fast spindles” (250 - 500 Hz) is strongly associated with epileptogenic tissue. HFOs can be recorded with depth electrodes, but recently it has been shown that HFOs can also be demonstrated with non invasive MEG virtual sensors [2]. HFOs are found mainly in the vicinity of the classic epileptiform discharges. What is the relation between the focus with spikes and HFOs on the one hand, and the pathological hubs on the other hand? Remarkably, there is evidence that the focus and the pathological hub do not coincide. In fact, the presence of HFOs and typical hub features is even anticorrelated, at least at relatively short distances [23, 24]. Even so it is known that both the removal of the actual epileptic focus, as well as removal of the pathological hub areas, have a favourable effect on epilepsy surgery outcome. Before considering a possible explanation of this paradox, it is worthwhile to devote some attention to global network changes in epilepsy.

Global network changes in epilepsy

As discussed above there are many indications that epilepsy is characterized by changes in global brain networks [3, 25]. These changes consist of an increase of local connectivity, a decrease of global integration, and damage to, or a dysfunction of physiological hubs, in particular in the so-called default mode network. These global changes concern structural as well as functional brain networks. It is important to note that these global network changes are associated in particular with longstanding, chronic epilepsy [26]. In addition there are indications that global network changes are associated with, or may even be responsible for cognitive disturbances in patients with epilepsy [27, 28]. In this respect epilepsy shows some remarkable similarities to other chronic neurological conditions such as Alzheimer’s and Parkinson’s disease, multiple sclerosis and brain tumors, where cognitive dysfunction is associated with a loss of integration and damage to the default mode network [4]. Possibly the global brain network changes are caused by damage due to repetitive hyperactiva-

tion during recurrent epileptic seizures. Again, there is a remarkable analogy with hyperactivation induced network damage described as a putative mechanism in Alzheimer's disease [29]. Apparently, hubs are involved in epilepsy in two rather different ways: (i) local, pathological hubs in the vicinity of the actual focus appear to form part of a local epileptogenic network, and are responsible for spreading epileptic activity to the rest of the brain; (ii) physiological hubs, in particular in the default mode network, are damaged by repetitive seizures, and may underlie cognitive disturbances.

A focal - local - global model of epilepsy

Is it possible to integrate the classic concept of epilepsy as activity that arises in a hyperexcitable focus with the newer ideas about the role of networks? The relationship can perhaps be understood with a simple scheme in which three levels are considered in relation to each other (Figure 1).

The most basic level is the classic epileptic focus, a circumscribed area with a disturbed balance between excitation and inhibition. This focus generates abnormal activity in the form of epileptiform abnormalities and HFOs, in particular fast ripples. This activity can be detected in some of the patients with neurophysiologic techniques, invasive or non invasive, and possibly also

with newer techniques such as MEG virtual sensors. The second level is the local epileptogenic network. This is a circumscribed network, that will include the actual epileptic focus, and will be limited to (part of) a lobe, or an area involving two nearby lobes. It is important to realize that under normal conditions the epileptic focus is surrounded by a "ring" of inhibition, preventing the spreading of epileptic activity to the rest of the local network and the start of a seizure. The local network is thus important for inhibiting the epileptic focus, but it is also the first brain area that gets involved if seizure activity breaks through the inhibitory ring and starts to spread. The highest level in the scheme is formed by the rest of the global brain network. There are indications that pathological hubs are located at the border between the local and the global network [30]. Normally, these pathological hubs are not excessively activated (the epileptic focus is surrounded by an inhibitory ring, and cannot communicate directly with the pathological hub). However, when the inhibition breaks down, seizure activity can spread through the local network and reach the pathological hub, and spread rapidly through the global network from here, giving rise to a generalized seizure. If this happens repeatedly, chronic damage in the global network may result, with loss of integration and cognitive disturbances.

For now, this three-layer model of epilepsy (focal-local-global) is only a hypothesis. However, there are

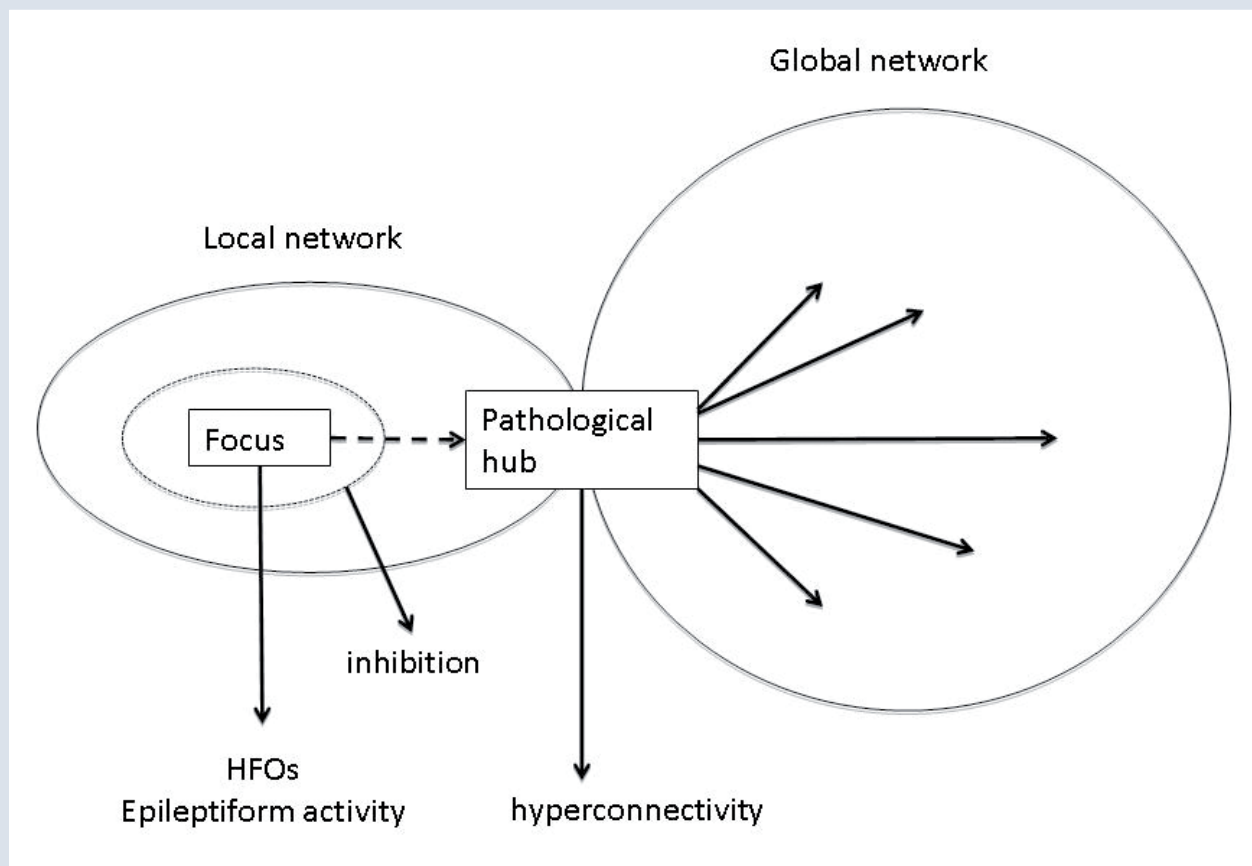


Figure 1: A focal-local-global model of epilepsy

a few clinically relevant aspects. The model could be of interest from the point of view of diagnosis, (surgical) treatment, and prognosis. From a diagnostic perspective it is interesting to note that the pathological hubs will not be characterized by epileptiform activity or HFOs, but by abnormal hypersynchronization or hyper connectivity. These hub phenomena can be detected with neurophysiologic techniques such as MEG and invasive or non-invasive EEG [31]. This suggests that even in EEGs without epileptiform abnormalities it may be possible to demonstrate changes that are suggestive of pathological hubs [32]. This could support a diagnosis of epilepsy. In two recent studies it has been shown that this is indeed possible in routine interictal EEGs in adults or children suspected of epilepsy [31, 32]. Furthermore, even though the epileptic focus and the pathological hub do not coincide, it is quite likely they are located in the same area, probably the same lobe, and very likely the same hemisphere. Detection of pathological hubs could therefore, even in the absence of epileptiform abnormalities, contribute to lateralization and localization of the epileptic area. In the context of epilepsy surgery the focal-local-global model is of interest since it makes clear what has to be removed at a minimum to abort the epileptic seizures (this is in fact a definition of the epileptogenic zone): according to the model removal of the pathological hub, and/or the connections between the hub and the focus, should also result in a decrease or disappearance of generalized seizures. This is important when the focus itself is located in or near eloquent cortex and cannot be removed safely. Finally, global network changes can be useful as a marker for brain damage due to chronic epilepsy, and the corresponding cognitive deficits [27, 28]. A better understanding of the chronic global effects of epilepsy could point the way toward more effective treatments directed at prevention of global brain damage [33].

References

- Jacobs J, Staba R, Asano E et al. High-frequency oscillations (HFOs) in clinical epilepsy. *Prog Neurobiol* 2012; 98: 302-315
- Van Klink N, Hillebrand A, Zijlmans M. Identification of epileptic high frequency oscillations in the time domain by using MEG beamformer-based virtual sensors. *Clin Neurophysiol* 2015; Jun 16. pii: S1388-2457(15)00637-9. doi: 10.1016/j.clinph.2015.06.008. [Epub ahead of print]
- Van Diessen E, Diederens SJ, Braun KP et al. Functional and structural brain networks in epilepsy: what have we learned? *Epilepsia* 2013; 54: 1855-1865
- Stam CJ. Modern network science of neurological disorders. *Nat Rev Neurosci* 2014; 15: 683-695
- Barabasi AL, Albert R. Emergence of scaling in random networks. *Science* 1999; 286: 509-512
- Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature* 1998; 393: 440-442
- Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci* 2012; 13: 336-349
- Crossley NA, Mechelli A, Scott J et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* 2014; 137: 2382-2395
- Netoff T, Clewley R, Arno S et al. Epilepsy in small-world networks. *J Neurosci* 2004; 24: 8075-8083
- Morgan RJ, Soltesz I. Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *Proc Natl Acad Sci U S A* 2008; 105: 6179-6184
- Ponten SC, Bartolomei F, Stam CJ. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin Neurophysiol* 2007; 118: 918-927
- Kramer MA, Kolaczuk ED, Kirsch HE. Emergent network topology at seizure onset in humans. *Epilepsy Res* 2008; 79: 173-186
- Schindler KA, Bialonski S, Horstmann MT et al. Evolving functional network properties and synchronizability during human epileptic seizures. *Chaos* 2008; 18: 033119
- Ponten SC, Douw L, Bartolomei F et al. Indications for network regularization during absence seizures: weighted and unweighted graph theoretical analyses. *Exp Neurol* 2009; 217: 197-204
- Liao W, Zhang Z, Pan Z et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One* 2010; 5: e8525
- Otte WM, Dijkhuizen RM, van Meer MP et al. Characterization of functional and structural integrity in experimental focal epilepsy: reduced network efficiency coincides with white matter changes. *PLoS One* 2012; 7: e39078
- Horstmann MT, Bialonski S, Noennig N et al. State dependent properties of epileptic brain networks: comparative graph-theoretical analyses of simultaneously recorded EEG and MEG. *Clin Neurophysiol* 2010; 121: 172-185
- Bernhardt BC, Hong S, Bernasconi A, Bernasconi N. Imaging structural and functional brain networks in temporal lobe epilepsy. *Front Hum Neurosci* 2013; 7: 624
- Van Diessen E, Zweiphenning WJ, Jansen FE et al. Brain network organization in focal epilepsy: A systematic review and meta-analysis. *PLoS One* 2014; 9: e114606
- Ortega GJ, Menendez de la Prida L, Sola RG, Pastor J. Synchronization clusters of interictal activity in the lateral temporal cortex of epileptic patients: intraoperative electrocorticographic analysis. *Epilepsia* 2008; 49: 269-280
- Varotto G, Tassi L, Franceschetti S et al. Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. *Neuroimage* 2012; 61: 591-598
- Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. *Epilepsia* 2011; 52: 84-93
- Van Diessen E, Hanemaaijer JI, Otte WM et al. Are high frequency oscillations associated with altered network topology in partial epilepsy? *Neuroimage* 2013; 82: 564-573
- Ibrahim GM, Anderson R, Akiyama T et al. Neocortical pathological high-frequency oscillations are associated with frequency-dependent alterations in functional network topology. *J Neurophysiol* 2013; 110: 2475-2483
- DeSalvo MN, Douw L, Tanaka N et al. Altered structural connectome in temporal lobe epilepsy. *Radiology* 2014; 270: 842-848
- Van Dellen E, Douw L, Baayen JC et al. Long-term effects of temporal lobe epilepsy on local neural networks: a graph theoretical analysis of corticography recordings. *PLoS One* 2009; 4: e8081
- Vaessen MJ, Jansen JF, Vlooswijk MC et al. White matter network abnormality

- malities are associated with cognitive decline in chronic epilepsy. *Cereb Cortex* 2012; 22: 2139-2147
28. Vlooswijk MC, Vaessen MJ, Jansen JF et al. Loss of network efficiency associated with cognitive decline in chronic epilepsy. *Neurology* 2011; 77: 938-944
29. De Haan W, Mott K, van Straaten EC et al. Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. *PLoS Comput Biol* 2012; 8: e1002582
30. Yasuda CL, Chen Z, Beltramini GC et al. Aberrant topological patterns of brain structural network in temporal lobe epilepsy. *Epilepsia* 2015 Nov 4; doi: 10.1111/epi.13225 [Epub ahead of print]
31. Douw L, de Groot M, van Dellen E et al. 'Functional connectivity' is a sensitive predictor of epilepsy diagnosis after the first seizure. *PLoS One* 2010; 5: e10839
32. Van Diessen E, Otte WM, Braun KP et al. Improved diagnosis in children with partial epilepsy using a multivariable prediction model based on EEG network characteristics. *PLoS One* 2013; 8: e59764
33. Van Dellen E, de Witt Hamer PC, Douw L et al. Connectivity in MEG resting-state networks increases after resective surgery for low-grade glioma and correlates with improved cognitive performance. *Neuroimage Clin* 2012; 2: 1-7

Address for correspondence:

Prof. Cornelis Jan Stam

Department of Clinical Neurophysiology

VU University Medical Center

De Boelelaan 1118

NL 1081 HV Amsterdam

Tel. 020 4440727

Fax 020 4444816

CJ.Stam@vumc.nl