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NEUROPSYCHOLOGICAL PERFORMANCE AND FUNCTIONAL MRI FINDINGS IN CHILDREN WITH NON-LESIONAL TEMPORAL LOBE EPILEPSY

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UNIVERSITY OF OULU, FACULTY OF MEDICINE,
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LÄNSI-POHJA CENTRAL HOSPITAL, DEPARTMENT OF PAEDIATRICS

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Abstract

The purpose of the present work was to investigate whether children with non-lesional temporal lobe epilepsy (TLE) have deficits in neuropsychological performance and whether the possible deficits can be investigated using functional magnetic resonance imaging (fMRI).

In this population-based study, 21 children aged 8-15 with non-lesional TLE and a normal intelligence quotient were evaluated and compared with 21 healthy, age- and gender-matched controls. Neuropsychological assessments, clinical examinations, electroencephalography (EEG) and structural and functional MRI were performed on all the subjects. Three fMRI methods were used: resting-state regional homogeneity, resting-state functional connectivity and task-induced blood oxygenation level-dependent activation.

The patients with non-lesional TLE showed good neuropsychological performance on average, although the girls were found to have significant problems in several neuropsychological tests. The deficits were not restricted to elements of performance involving the classical temporal lobe memory system but were also found in tests requiring frontal and parietal lobe functioning. Early onset of epilepsy and duration of epilepsy had significant negative effects on neuropsychological performance.

All the fMRI methods detected significant functional differences between the TLE patients and the healthy controls, not only in the temporal lobes but also in broad networks extending to the frontal, parietal and thalamic areas. These differences seemed to differ markedly in location between the TLE patients depending on the interictal EEG findings.

Neuropsychological performance results were supported by the fMRI findings, implying that TLE should be regarded as a widespread disruption of the brain networks and not just malfunction of a single region in the brain within these networks. This needs to be taken into consideration when evaluating learning abilities among TLE patients even at an early stage in epilepsy.

Keywords: brain networks, child, functional connectivity, functional magnetic resonance imaging, neuropsychological performance, regional homogeneity, temporal lobe epilepsy

Mankinen, Katariina, Neuropsykologinen suoriutuminen ja toiminnallisen magneettikuvauksen löydökset lapsilla, joilla on tuntemattomasta syystä aiheutuva ohimolohkoepilepsia.

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Tiivistelmä

Tutkimuksen tarkoituksena oli selvittää onko lapsilla, jotka sairastavat tuntemattomasta syystä aiheutuvaa ohimolohkoepilepsiaa, neuropsykologisia ongelmia ja aiheuttavatko mahdolliset ongelmat aivojen toiminnallisessa magneettikuvauksessa nähtäviä muutoksia.

Tähän väestöpohjaiseen tutkimukseen otettiin 21 tuntemattomasta syystä ohimolohkoepilepsiaa sairastavaa normaaliälyistä 8-15-vuotiaista lasta ja verrattiin heitä 21 terveeseen, ikä- ja sukupuolivakioituun kontrollihenkilöön. Kaikille tutkimukseen osallistuneille tehtiin neuropsykologinen tutkimus, kliininen tutkimus, aivosähkökäyrä sekä rakenteellinen ja toiminnallinen aivojen magneettikuvaus.

Toiminnallisessa magneettikuvauksessa käytettiin veren happipitoisuudesta riippuvaista (engl. blood oxygenation level-dependent) kontrastia kuvantamaan levossa aivojen paikallista homogeniteettia (engl. regional homogeneity) ja toiminnallista kytkennällisyyttä (engl. functional connectivity) sekä kognitiivisten tehtävien herättämiä aktivaatio-vasteita.

Tuntemattomasta syystä ohimolohkoepilepsiaa sairastavien lasten neuropsykologinen suoriutuminen oli keskimäärin hyvää, vaikkakin tytöillä oli nähtävillä tilastollisesti merkitseviä ongelmia useissa eri testeissä. Ongelmat eivät rajoittuneet pelkästään klassisiin ohimolohkoalueen muistitoimintoihin, vaan niitä havaittiin myös otsa- ja päälakilohkojen toimintoja edellyttävissä testeissä. Varhainen sairastumisikä ja epilepsian kesto heikensivät suoriutumista tilastollisesti merkitsevästi osatesteissä, joissa tarvittiin näönvaraisen hahmottamisen taitoja, psykomotorista nopeutta ja työmuistia.

Ohimolohkoepilepsiaa sairastavien ja terveiden kontrollien aivoissa löydettiin toiminnallisia eroja kaikilla toiminnallisen magneettikuvauksen menetelmillä. Eroja ei todettu ainoastaan ohimolohkoissa, vaan niitä löytyi myös otsa- ja päälakilohkoon sekä tyvitumakealueelle ylettyvissä laaja-alaisissa hermoverkostoissa. Epilepsiapotilailla erojen paikantuminen riippui kohtaustenvälisestä aivosähkökäyrälöydöksestä.

Neuropsykologisen suoriutumisen tulokset tukevat toiminnallisen magneettikuvauksen löydöksiä kuvastaen temporaaliepilepsian olevan laaja-alainen hermoverkostojen häiriö eikä pelkästään tietyn aivoalueen toiminnan häiriö. Tämä tulee huomioida arvioitaessa ohimolohkoepilepsiaa sairastavien lasten oppimiskykyä jo epilepsian alkuvaiheessa.

Asiasanat: hermoverkostot, lapsi, neuropsykologinen suoriutuminen, ohimolohkoepilepsia, paikallinen homogeniteetti, toiminnallinen kytkennällisyys, toiminnallinen magneettikuvaus

To lifelong learning

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Oulu, October 2013 Katariina Mankinen

Abbreviations

BOLD	blood oxygenation level-dependent
CBF	cerebral blood flow
DMN	default mode network
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
ICA	independent component analysis
IQ	intelligence quotient
LD	learning disorders
LTLE	lateral temporal lobe epilepsy
MTLE	mesial temporal lobe epilepsy
MTS	mesial temporal sclerosis
MRI	magnetic resonance imaging
NBR	negative blood oxygenation level-dependent response
PBR	positive blood oxygenation level-dependent response
ReHo	regional homogeneity
RSN	resting-state network
TLE	temporal lobe epilepsy

List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals.

I Mankinen K, Harila M, Rytky S, Pokka T & Rantala H (2013) Neuropsychological performance in children with temporal lobe epilepsy having normal MRI findings. Eur Jour Ped Neurol. In press. DOI http://dx.doi.org/10.1016/j.ejpn.2013.08.005

II Mankinen K, Long X-Y, Paakki J-J, Harila M, Rytky S, Tervonen O, Nikkinen J, Starck T, Remes J, Rantala H, Zang Y-F & Kiviniemi V (2011) Alterations in regional homogeneity of baseline brain activity in pediatric temporal lobe epilepsy. Brain Res 1373: 221–229.

III Mankinen K, Jalovaara P, Paakki J-J, Harila M, Rytky S, Tervonen O, Nikkinen J, Starck T, Remes J, Rantala H & Kiviniemi V (2012) Connectivity disruptions in resting-state functional brain networks in children with temporal lobe epilepsy. Epil Res 100: 168–178.

IV Mankinen K, Ipatti P, Harila M, Nikkinen J, Paakki J-J, Rytky S, Starck T, Remes J, Tokariev M, Carlson S, Tervonen O, Rantala H & Kiviniemi V (2013) Reading, listening and memory-related brain activity in children with early-stage non-lesional temporal lobe epilepsy - an fMRI study. Manuscript.

Contents

1 Introduction

Epilepsy – defined as recurrent, unprovoked seizures – is the most common neurological disorder in childhood (Ross 1994). It is a highly complex brain disorder with heterogeneous aetiologies and a wide range of manifestations and forms of clinical evolution. The fundamental pathophysiological mechanisms of epileptogenesis are still not fully understood (Terry *et al.* 2012), and the International League Against Epilepsy (ILAE) has recently proposed a revised approach to the description of seizures and types of epilepsy that is moving towards a mechanism-based classification (Berg & Scheffer 2011). In this new proposal the long-standing dichotomy between "primary generalized" and "focal" seizures is redefined as one between seizures occurring in bilateral networks and those occurring within networks that are limited to one hemisphere and either discretely localized or more widely distributed (Berg *et al.* 2010), reflecting the viewpoint that the core foundation of epilepsy lies behind the brain networks and network structure (Laufs 2012, Terry *et al.* 2012).

Children with epilepsy are known to run a greater risk of developing learning disorders (LD) with long-standing consequences, regardless of the type of epilepsy or the way in which learning disorders are defined (Mitchell *et al.* 1991, Sillanpaa *et al.* 1998, Williams 2003, Fastenau *et al.*, 2008, Dunn *et al.* 2010). Reported rates of LD among paediatric epilepsy patients vary in the range 5–50% between studies (Aldenkamp *et al.* 1990, Beghi *et al.* 2006, Fastenau *et al.* 2008). LD may precede epilepsy (Oostrom *et al.* 2003, Berg *et al.* 2005) or may arise in the course of epilepsy (Helmstaedter & Elger 2009).

Functional magnetic resonance imaging (fMRI) has become a leading method for investigating human cognition and the functional organization of brain networks. It has increasingly been used with patients having intractable epilepsy, for characterizing cognitive changes and providing information for use in clinical practice when epilepsy surgery is being considered. Whether the functional changes are detectable in new-onset or early-stage epilepsy remains an open question, however, and therefore detailed clinical information combined with advanced functional neuroimaging at an early stage of epilepsy may provide a better understanding of both epileptogenesis and the development of associated learning difficulties.

2 Review of the literature

2.1 Temporal lobe epilepsy

2.1.1 Definition, epidemiology and aetiology

Definition

Temporal lobe epilepsy (TLE) is a focal epilepsy characterized by recurrent epileptic seizures arising from one or both temporal lobes of the brain. Two main types are recognized according to the International League Against Epilepsy (Engel Jr 2001): mesial temporal lobe epilepsy (MTLE), originating from the hippocampus, parahippocampal gyrus and amygdala located in the inner aspect of the temporal lobe, and lateral temporal lobe epilepsy (LTLE) originating from the neocortex on the outer surface of the temporal lobe.

Epidemiology

Despite extensive research into the epidemiology of epilepsy, there is little information on exact incidence or prevalence figures for paediatric TLE, since patients with all types of focal epilepsy are often grouped together in epidemiological studies. As average annual incidence figures for all epilepsies in children from birth to age 15 across populations are in the range 50–70/100 000 (Cowan 2002) and two-thirds of all epilepsies are focal (Panayiotopoulos 2007), with TLE constituting about one-third of all focal epilepsies (Loiseau *et al.* 1991, Manford *et al.* 1992, Sillanpaa *et al.* 1999), it is possible to calculate the incidence of paediatric TLE to be 11–15/100 000/year. Similarly, calculating from a previous Finnish study (Eriksson & Koivikko 1997), the prevalence of all focal epilepsies among children aged 6–15 years would be 2.3/1000 and the prevalence of TLE in that age group would therefore be 0.8/1000.

Aetiology

The aetiology of paediatric temporal lobe epilepsy differs from that of the relatively homogeneous syndrome of adult TLE, where mesial temporal sclerosis

(MTS) is the most common aetiology (Malmgren & Thom 2012, Nickels *et al.* 2012).

Three aetiological subgroups have been distinguished on evidence from two community-based cohorts of children with new-onset TLE aged 0–15 years (Harvey *et al.* 1997, Sztriha *et al.* 2002), the largest of which consists of children with normal neuroimaging and no significant past history. This covered approximately half the patients in each cohort. The second subgroup, accounting for 16–27% of cases, consisted of children with focal congenital brain abnormalities such as cortical dysplasia, migrational disorder, hamartoma or a low-grade tumour, while the third subgroup, which accounted for 23–29% of the cohorts, had hippocampal sclerosis or a significant antecedent event such as a focal or prolonged febrile seizure or intracranial infection as the aetiological background.

In contrast to adult TLE patients, MTS is a rare finding in paediatric TLE in all age groups and is seen more often in older children and adolescents than in infants and younger children (Bourgeois 1998). Reported rates for MTS in paediatric patients with intractable TLE have varied between 15–50% (Duchowny *et al.* 1992, Salanova *et al.* 1999, Smyth *et al.* 2007, Kasasbeh *et al.* 2012), while approximately two-thirds of all adults with intractable TLE have MTS (Berg 2008).

If MTS is present in children it is more frequently associated with an extrahippocampal pathology such as cortical dysplasia or low-grade tumour, constituting what is generally called “dual pathology”. This has been reported in 30–80% of all cases of MTS in children (Mohamed *et al.* 2001, Bocti *et al.* 2003, Lee *et al.* 2010), whereas the proportion in adults has been 15–30% (Harroud *et al.* 2012).

2.1.2 Symptoms and diagnosis

Symptoms

The semiology of temporal lobe seizures in children is dependent on age and differs from that seen in adults. In infants and young children behavioural arrest, decreased motor activity, spasms and tonic, bilaterally symmetrical extensor stiffening are common clinical symptoms (Acharya *et al.* 1997, Hamer *et al.* 1999). Secondary generalization of seizures is uncommon during childhood

(Dravet *et al.* 1989, Rodriguez *et al.* 2007, Sisodiya *et al.* 2009). The motor manifestations decrease with increasing age, and dystonic posturing is seen more often in the form of contralateral movements of the body (Brockhaus & Elger 1995). Automatisms are commonly seen in all age groups, being discrete and mostly orofacial in younger patients and increasing in complexity with age. Auras, which are a common feature in adult TLE patients, are rare or are difficult to recognize in infants and young children, whereas they are commonly described in older children and adolescents (Ray & Kotagal 2005).

The clinical manifestations of seizures start to resemble more those of adult TLE patients with increasing age, whereupon the typical features of seizures arising from the mesial temporal structures come to include characteristic auras, automatisms, motor arrest and alteration of consciousness followed by amnesia. Ictal motor symptoms and postictal confusion can occur, depending on the spread and duration of the seizures (Wieser 2004, Blair 2012), and MTLE seizures can typically last over a minute, followed by gradual recovery (ILAE 1989, Foldvary *et al.* 1997).

Common auras in MTLE include rising epigastric and substernal sensations, emotional phenomena such as fear and sadness, illusions of familiarity and strangeness, non-specific sensations (i.e. auras that are "difficult to describe") and autonomic symptoms. Olfactory-gustatory auras are rarer findings. Abdominal pain associated with fear is also encountered in children. Automatisms are typically oroalimentary or manual, and unilateral motor signs are frequently seen as ipsilateral contractions of the face and mouth, head deviations or bilateral motor phenomena in the face or axial muscles (ILAE 1989, Blair 2012).

LTLE seizures are less common and therefore less well characterized than MTLE seizures (Blair 2012). They are typically shorter, and secondary generalization is more common. Neocortical seizures often begin with staring, while automatisms and epigastric phenomena are less common symptoms (ILAE 1989, Foldvary *et al.* 1997, Gil-Nagel & Risinger 1997). Auditory hallucinations/illusions, dreamy states, visual misperceptions, language disorders and focal sensory-motor phenomena represent the LTLE seizure type in terms of the ILAE criteria (ILAE 1989).

Diagnosis

The diagnosis of TLE is based on a typical clinical seizure semiology of temporal lobe origin unprovoked by any immediately identifiable cause. The interictal

electroencephalogram (EEG) can be normal, or it may show slight or marked asymmetry in the background activity, temporal spikes, sharp waves and/or slow waves that are unilateral or bilateral and synchronous, but sometimes also asynchronous. These findings are not always confined to the temporal region (ILAE 1989). It is important to note that ictal and interictal EEG recordings in children may be poorly localized due to incomplete brain maturation (Nickels *et al.* 2012).

Ictal surface EEG findings in paediatric TLE can vary depending on the age of the child, so that they can reveal generalized or multifocal epileptiform discharges without clear focality in infants and younger children, whereas in older children the ictal EEG onset consists mostly of rhythmic activity over the temporal region (Yamamoto *et al.* 1987, Brockhaus & Elger, 1995).

2.1.3 Temporal lobe epilepsy and neuropsychological performance

Neuropsychological assessment in cases of TLE is usually carried out as part of a surgical evaluation and has therefore been well studied in patients who have intractable epilepsy. Epilepsy surgery needs to be considered only in a minority of cases of childhood-onset TLE (Berg *et al.* 2003, Sillanpaa & Schmidt 2006, Berg 2008), however, which implies that most of our evidence on cognitive profiles in paediatric TLE is derived from highly selected patient groups (Nickels *et al.* 2012). According to the results of a number of preoperative studies, the most prominent deficits are found in verbal and visual memory (Gleissner *et al.* 2002, Mabbott & Smith 2003, Nolan *et al.* 2004, Gonzalez *et al.* 2007, Guimaraes *et al.* 2007, Jambaque *et al.* 2007) and also to some extent in executive functions (Igarashi *et al.* 2002, Guimaraes *et al.* 2007, Rzezak *et al.* 2007). It seems that deficits in the language domain are not restricted to verbal memory, and that problems with reading ability, sentence comprehension, word fluency and naming have also been detected (Lendt *et al.* 1999, Chaix *et al.* 2006, Guimaraes *et al.* 2007).

Studies of adult TLE patients have shown that an early age at the onset of recurrent seizures is associated with more severe and more widely compromised neuropsychological performance than a later age at onset. This finding was first reported as early as 1924 (Fox 1924) and has been confirmed in several adult studies (Dikmen *et al.* 1977, Dodrill & Matthews 1992, Hermann *et al.* 2002, Kaaden & Helmstaedter 2009). The same correlation has been reported in some

studies of younger patients with complex focal seizures or other types (O'Leary *et al.* 1983, Schoenfeld *et al.* 1999, Cormack *et al.* 2007).

2.1.4 Temporal lobe epilepsy and learning disorders

Specific investigations into learning difficulties (LD) among children with TLE are lacking, since studies of LD and epilepsy typically include patients with many types of epilepsy. According to the existing data, children with epilepsy are known to run a greater risk of developing learning disorders with long-standing consequences regardless of the type of epilepsy and the definition used for learning disorders (Mitchell *et al.* 1991, Sillanpaa *et al.* 1998, Williams 2003, Fastenau *et al.* 2008, Dunn *et al.* 2010). Reported rates of LD among paediatric epilepsy patients vary in the range 5–50% (Aldenkamp *et al.* 1990, Beghi *et al.* 2006, Fastenau *et al.* 2008), and LD may precede epilepsy (Oostrom *et al.* 2003, Berg *et al.* 2005, Hermann *et al.* 2006, Bhise *et al.* 2010) or arise during the course of epilepsy (Helmstaedter & Elger 2009).

The results of aetiological investigations that go beyond LD are inconsistent. It seems that LD among children with epilepsy is the result of complex interactions between several variables, including epilepsy-related and medication-related risk factors, neuropsychological deficits and the family environment (Bailet & Turk 2000, Fastenau *et al.* 2004, Dunn *et al.* 2010, Jones *et al.* 2010, Hermann *et al.* 2012). Some studies have shown that a symptomatic aetiology for epilepsy is a major predictor of academic underachievement (Berg *et al.* 2004, Aldenkamp *et al.* 2005, Berg *et al.* 2005), but the risk factors for LD are less clearly defined in children with no additional neurological deficits.

Neuropsychological functioning has been shown to be a predictor of academic achievement both in children with epilepsy and in healthy controls (Fastenau *et al.* 2004, Dunn *et al.* 2010). As neuropsychological performance in children with intractable TLE has been relatively well studied, with the findings described above, it is apparent that this subgroup of paediatric TLE patients has significant problems in learning. It is largely unknown, however, to what extent LD occur among non-intractable TLE patients.

2.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a widely used non-invasive neuroimaging technique that can detect and localize brain areas engaged in

performing a specific task. After its introduction 20 years ago (Belliveau *et al.* 1991, Bandettini *et al.* 1992, Kwong *et al.* 1992, Ogawa *et al.* 1992), it has become a leading research tool for investigating the cognitive functioning of the human brain. The knowledge gained from this vast amount of brain activation research has enabled neuroscientists to identify the cortical areas underlying memory, language, decision making and attention both in healthy populations and in the presence of various neurological disorders.

2.2.1 Blood oxygenation level-dependent contrast

The fMRI technique typically makes use of fast T2* -weighted imaging sequences such as gradient recalled echo-planar imaging (Mansfield 1977) or spiral k-space trajectory (Glover 2001) acquisition. T2* images are sensitive to changes in MRI susceptibility that reflect alterations in blood oxygenation. This functional contrast is generally referred to as blood oxygenation level-dependent (BOLD) contrast, as first discovered by Ogawa *et al.* (1990a, 1990b, Ogawa & Lee 1990). The physical basis for these BOLD contrast sequences lies in the oxygenation-dependent magnetic susceptibility of haemoglobin. Deoxyhaemoglobin is paramagnetic, causing slightly attenuated signal intensity in those MRI image voxels that contain deoxygenated blood. Neuronal activation during performance of a specific task induces an increase in metabolic demand and results in increased cerebral blood flow (CBF) (Fox *et al.* 1988, Fox & Raichle 1986) to the activated brain area to meet that demand. Within a few seconds the increased CBF overcompensates for the decrease in oxygen, delivering an oversupply of oxygenated blood. The newly perfused area is thus saturated with more oxygenated blood and the decrease in the deoxyhaemoglobin content translates into an increased MRI signal secondarily reflecting neuronal activation. The BOLD effect is most pronounced in the venous capillaries and the surrounding brain parenchyma (Cohen & Bookheimer 1994).

2.2.2 Activation

Neural activation during a cognitive task is reflected as an increase in BOLD signal, referred to also as a positive BOLD response (PBR). It is the investigation of these PBRs that has formed the basis for fMRI studies. Despite the extensive use of the method for mapping brain functions, the coupling mechanisms between neural cellular activity and BOLD signals are incompletely understood.

Experiments using combined imaging and intracortical electrophysiological measurements have nevertheless provide evidence to link PBR primarily to local field potentials that reflect the sum of inhibitory and excitatory postsynaptic potentials, and secondarily to action potential outputs (Logothetis *et al.* 2001, Logothetis & Wandell 2004, Mukamel *et al.* 2005). The modern, widely accepted hypothesis is that activation-induced blood changes are driven by the synaptic input to a certain brain region (Logothetis 2008, Ekstrom 2010) reflecting neural activity.

2.2.3 Deactivation

An often observed but less frequently reported fMRI signal is deactivation, also termed negative BOLD response (NBR), reflecting relative increases in deoxyhaemoglobin concentration that are detectable as decreases in the MRI signal. Such a response has been reported in visual (Shmuel *et al.* 2002, Bressler *et al.* 2007, Pasley *et al.* 2007), auditory (Laurienti *et al.* 2002) and somatosensory (Kastrup *et al.* 2008, Klingner *et al.* 2011, Liu *et al.* 2011, Schafer *et al.* 2012) regions of the brain. NBR is most commonly seen in extensive brain areas called default mode areas (see below), where it is detected only during the performance of demanding cognitive tasks or goal-directed behaviour (Fox *et al.* 2005). NBR can be detected in different brain regions or even within the same area during the performance of a given task, but its origin and its relationship to metabolic and neural responses are controversial and various hypotheses have been proposed for its occurrence (Moraschi *et al.* 2012). Some researchers suggest that NBR is generated by vascular mechanisms, so that they regard it as a "blood stealing" phenomenon (Harel *et al.* 2002), based on the idea that the blood flow is redirected to the activated region and away from adjacent inactive regions (Woolsey *et al.* 1996). Alternatively, the "blood sharing" theory proposes that the reduced blood flow in the NBR areas is controlled by specific neuronal populations that regulate blood flow via neurons of the autonomic nervous system or by inhibitory interneurons acting directly on blood vessels (Smith *et al.* 2004). Animal studies have revealed a tight coupling between NBRs and reduced neuronal activity (Boorman *et al.* 2010, Shmuel *et al.* 2006) or enhanced inhibition within sensory systems (Devor *et al.* 2007), and a correlation has been demonstrated in humans between the NBR and changes in the sensory threshold (Kastrup *et al.* 2008, Klingner *et al.* 2010). The intensity of the NBR has also shown to be coupled to the concentration of the inhibitory neurotransmitter

GABA in the DMN (Northoff *et al.* 2007). These findings suggest that an NBR reflects a suppression of neural activity and can therefore be used for mapping neuronal functionality. It is most probable, however, that it is not of a single origin and that it reflects a suppression of neuronal activity in some regions and is of haemodynamic origin in others (Liu *et al.* 2011, Moraschi *et al.* 2012).

2.2.4 Resting-state networks

Since the introduction of fMRI, attention has been drawn in a number of studies to the occurrence of spontaneous, low frequency (0.01–0.1 HZ) coherent BOLD signal fluctuations in the resting brain in the absence of any task or stimulation. These spontaneous signal changes which have been taken to represent the brain´s resting-state activity (Biswal *et al.* 1995, Lowe *et al.* 1998, Kiviniemi *et al.* 2000, Cordes *et al.* 2001, Gusnard *et al.* 2001) are synchronized in time between anatomically distant but functionally connected brain regions, termed resting-state networks (RSNs) (Beckmann *et al.* 2005, Damoiseaux *et al.* 2006, Fox & Raichle 2007) and are thought to arise from fluctuations in neurovascular brain activity and metabolic demands in the resting brain that are unrelated to cardiac or respiratory effects (Birn *et al.* 2006, De *et al.* 2006). Setting out from Biswal´s first observation that these resting-state BOLD signal fluctuations define relationships between motor regions (Biswal *et al.* 1995), further research has revealed multiple brain regions that correlate in their time courses, commonly referred to as functionally connected RSNs (Fox & Greicius 2010).

A meta-analysis of nearly 1700 activation studies and brain resting-state analyses have shown that most of the functional variance in the human brain cortex is covered by a set of 42 detectable RSNs (Kiviniemi *et al.* 2009, Smith *et al.* 2009). These form units that mediate and control brain functions that account for sensorimotor function (Biswal *et al.* 1995, Lowe *et al.* 1998, De *et al.* 2005, Fox *et al.* 2006a, Kiviniemi *et al.* 2009, Smith *et al.* 2009) , visual (Lowe *et al.* 1998, Cordes *et al.* 2000) and auditory (Cordes *et al.* 2000) stimulus processing, memory (Hampson *et al.* 2006, Hampson *et al.* 2010), language (Cordes *et al.* 2000, Koyama *et al.* 2010), attention (Fox *et al.* 2006b) and a set of regions making up a default mode network that routinely increase activity during rest and reduce it during attention-demanding tasks (Raichle *et al.* 2001).

Characterization of these RSNs has improved our understanding of the functional topography of the brain and provided explanations for the large set of brain region involvement data obtained from task-evoked fMRI studies.

Spontaneous resting-state activity has been shown to continue during sleep (Fukunaga *et al.* 2006) and even under anaesthesia (Kiviniemi *et al.* 2000, Kiviniemi *et al.* 2003, Greicius *et al.* 2008), suggesting that it must have a fundamental role in brain function. Since resting-state imaging requires no task performance and makes minimal demands on the imaged subjects, it has opened up a new possibility for studying young children and for comparing patient populations, thus providing new insights into maturational brain processes and the functional abnormalities underlying given diseases. This new knowledge could in turn lead to the identification of new treatments and drug targets, or could even provide a means of monitoring the effects of treatment in the future (Fox & Greicius 2010).

Of all the RSNs, the "default mode network" (DMN) is of special interest, since it is known to exhibit elevated neuronal activity during rest but deactivation during cognitive tasks (Buckner *et al.* 2007, Greicius *et al.* 2003). It is also metabolically the most active area in the resting brain (Raichle *et al.* 2001). The DMN includes frontal areas along the midline, lateral and medial parietal regions, extending into the posterior cingulate and retrosplenial cortex and medial temporal lobes (Buckner & Vincent 2007). The actual function of the DMN is unclear, but it is thought to be involved in the integration of cognitive and emotional processing, i.e. in internally directed mental activity, thoughts and monitoring of the world around us (Buckner *et al.* 2008). The episodic memory plays a pivotal role in this kind of mental processing which includes acts of remembering and retrieving past experiences (Buckner & Carroll 2007). The close connection of the DMN with memory systems in the frontal and medial temporal lobes affords an interesting approach to the study of memory and learning.

The DMN has been shown to be altered in various neurological and psychiatric diseases such as Alzheimer disease (Greicius *et al.* 2004, Rombouts *et al.* 2005), depression (Greicius *et al.* 2007), schizophrenia (Garrity *et al.* 2007, Liu *et al.* 2008, Whitfield-Gabrieli *et al.* 2009), autism spectrum diseases (Kennedy *et al.* 2006, Assaf *et al.* 2010, Weng *et al.* 2010) and attention deficit hyperactivity disorder (Cao *et al.* 2006, Uddin *et al.* 2008). Increasing numbers of studies have provided evidence that the DMN is also disrupted in epilepsy (Archer *et al.* 2003, Gotman *et al.* 2005, Kobayashi *et al.* 2006, Laufs *et al.* 2007, Morgan *et al.* 2008, Liao *et al.* 2010, Zhang *et al.* 2010), including both focal and generalized types.

2.2.5 Independent component analysis and resting-state functional connectivity

Fluctuations in brain activity can be separated into independent functional networks such as the primary sensory cortices and associative cortices using blind source separation methods. One of the most widely used of these is independent component analysis (ICA) (McKeown *et al.* 1998), which can distinguish relatively subtle intrinsic fluctuations in brain networks from other sources of variance in BOLD data such as physiological pulsations and head motion. ICA separates sources based on statistical independence by maximizing the non-Gaussian nature of the joint density distributions of the sources in an iterative process (c.f. http://research.ics.tkk.fi/ica/icademo). Each independent component is linked to a spatial map, with some maps reflecting noise components and others reflecting neuroanatomical systems (Kiviniemi *et al.* 2003).

If the resting-state activity of the brain is regarded as a 'cocktail party' of several participants interacting together continuously, ICA may be said to separate the individual participants from the continuous mumble of activity.

2.2.6 Regional homogeneity analysis

Regional homogeneity (ReHo) analysis is a fMRI analysis method developed by Zang et al (2004) that can be used to probe the most local connections in a given region of the brain. It enables analysis of the coherence of the resting-state BOLD signals from neighbouring voxels, making it possible to find coherent parts of the active brain areas (Zang 2004, Long *et al.* 2008). This data-driven method is suitable for exploring regional brain activity during rest, involving the examination of the degree of regional coherence of functional magnetic resonance imaging (fMRI) time courses. Regional homogeneity reflects the temporal homogeneity of regional BOLD signals regardless of their intensities. As the BOLD signals in fMRI reflect neural activity (Logothetis & Wandell 2004), an abnormal ReHo pattern is probably relevant to changes in the temporal aspects of neural activity in certain brain regions, and thus ReHo may be used to detect regions with abnormal activity (Yuan *et al.* 2008). ReHo analysis has been used successfully to detect alterations in subjects with ADHD, geriatric depression, schizophrenia and Alzheimer's dementia (Cao *et al.* 2006, Liu *et al.* 2006, He *et al.* 2007, Yuan *et al.* 2008).

2.3 fMRI in children

fMRI is well suited for mapping brain function in children, since it is non-invasive, safe and lacks radiation exposure. It is relatively repeatable, and thus provides an ideal way of imaging changes in brain function during development (Wilke *et al.* 2003, Freilich & Gaillard 2010).

Characterization of the relationship between cognitive function and neuronal activation in a developing brain nevertheless poses several methodological and interpretational challenges (Berl *et al.* 2006, Leach & Holland 2010, Luna *et al.* 2010). From the methodological point of view, preparation and compliance require special consideration when dealing with paediatric populations (Kotsoni *et al.* 2006, de Bie *et al.* 2010), as also do movement compensation (Yuan *et al.* 2009, Evans *et al.* 2010), the treatment of physiological noise and the inhomogeneity of the variance involved (Samanez-Larkin *et al.* 2008, Thomason *et al.* 2005). The use of developmentally appropriate paradigms is critical for successful fMRI performance (Byars *et al.* 2002, Kotsoni *et al.* 2006, Church *et al.* 2010). fMRI for studying resting-state networks has been conducted without anaesthesia even in pre-school age children (Byars *et al.* 2002, Gaillard *et al.* 2003a) and in newborns and infants (Doria *et al.* 2010, Fransson *et al.* 2007, Fransson *et al.* 2009, Fransson *et al.* 2011). Toddlers and young children, however, typically need anaesthesia, which can cause problems in interpreting the BOLD response (Altman & Bernal 2001).

2.3.1 BOLD signal changes during brain development

The BOLD signal response in the maturing brain may be influenced by many age-related and regionally variable anatomical and physiological changes that can last into early adulthood (Gaillard *et al.* 2001a, Wilke & Holland 2003), including synaptogenesis and pruning, myelination, alternations in cortical thickness and the overall increase in brain volume (Tau & Peterson 2010). The maturation process has an effect on the metabolic demands of neurons, and consequently on the cerebral blood flow, with the highest peak occurring in early childhood (Chugani *et al.* 1987). Although cerebral perfusion is tightly regulated, age-dependent cardiorespiratory changes may increase the physiological noise, thereby affecting the detection of the BOLD signal (Gaillard *et al.* 2001a).

As brain maturation is thought to occur through pruning and consolidation, an immature brain may produce a weak BOLD signal, since the synaptic

connections have not been reinforced by experience and the neural network is not consolidated. On the other hand, the BOLD signal from an immature brain may be more extensive due to unfinished pruning (Berl *et al.* 2006), or due to a child`s ability to use several strategies for cognitive processing (Booth *et al.* 2001, Dowker 2006).

The widely accepted "focalization" theory reflects the consolidation and synaptic reinforcement process described above, i.e. cortical regions that are activated are the same in children and in adults but there is a transition from diffuse, widespread low magnitude activation to more focal activation of greater magnitude with increasing age (Muller *et al.* 1998, Durston *et al.* 2006). The developmental change may be a more complex process than is assumed in the "focalization" theory, however (Brown *et al.* 2006, Poldrack 2010), since there are studies of many cognitive functions in which the magnitude of activation has been greater in children than in adults (Gaillard *et al.* 2000, Nelson *et al.* 2000, Gaillard *et al.* 2001b, Casey *et al.* 2002, Ahmad *et al.* 2003, Gaillard *et al.* 2003a), or has increased with age in some regions and decreased in other regions (Turkeltaub *et al.* 2003). Also, the extent of activation has sometimes proved to be greater in adults than in children, especially when assessing working memory (Rubia *et al.* 2000, Klingberg *et al.* 2002, Kwon *et al.* 2002) and verbal fluency (Gaillard *et al.* 2003b). One interpretational problem is that the BOLD signal cannot distinguish whether the greater activation is due to larger number of activated neurons or to increased activation within the same neurons (Karmiloff-Smith 2010). Taking all these observations into consideration, it may be said that BOLD signal findings in childhood are affected by numerous methodological, biological and experiental factors interacting in complex and multiple ways.

2.3.2 Functional connectivity during brain development

Results of examinations performed on preterm and term infants have shown that weakly formed RSNs involving several cortical and subcortical structures, the DMN and thalamic and cerebellar networks can be identified as early as the 26th week of gestation (Fransson *et al.* 2007, Fransson *et al.* 2009, Doria *et al.* 2010, Fransson *et al.* 2011). These observations support the hypothesis that resting-state activity is critical for the development of synaptic connections and the maintenance of synaptic homeostasis (Pizoli *et al.* 2011). RSNs increase in strength and quantity by the age of two years (Lin *et al.* 2008, Liu *et al.* 2008,

Gao *et al.* 2009, Damaraju *et al.* 2010) and integrate into a more cohesive, interconnected network during childhood (Fair *et al.* 2009).

2.4 fMRI in epilepsy

2.4.1 BOLD studies

The best studied application of traditional task-based fMRI to the evaluation of epilepsy has been the mapping of hemispheric language dominance and memory function prior to surgical intervention (Detre 2006, Swanson *et al.* 2007, Binder 2011). It is also well established that patients with left hemisphere epilepsy have a higher likelihood of atypical language reorganization (Hamberger & Cole 2011). A combination of fMRI tasks has proved to be more accurate in defining language dominance than a single task, and modifications of these methods can be used even in children (Gaillard *et al.* 2004, Wilke *et al.* 2006). Most sets of fMRI data on language and memory function in epilepsy nevertheless rely on the chronic stages of epilepsy and on adult studies (Hamberger & Cole 2011, Schmidt & Pohlmann-Eden 2011), so that it is not really known whether there are functional changes detectable at an early stage in epilepsy (Federico 2011).

Our knowledge of functional brain mapping in epilepsy is mainly based on interpretations of activation, whereas deactivation has attracted much less attention. Investigations combining EEG with fMRI (EEG-fMRI studies) have reported that the haemodynamic changes may precede epileptiform activity in the form of early activation in the epileptiform spike field (Makiranta *et al.* 2005, Hawco *et al.* 2007, Jacobs *et al*. 2007), which in one study (Jacobs *et al*. 2009) was followed by a later negative BOLD response (i.e. deactivation). The default mode regions have also been shown to be deactivated in response to both focal and generalized epileptiform discharges (Gotman *et al.* 2005, Carney *et al.* 2010, Siniatchkin *et al.* 2011, Fahoum *et al.* 2012).

2.4.2 Resting-state network connectivity studies

Studies of RSN functional connectivity in TLE have been focused on adult patients at the chronic stage of epilepsy, and the results have been variable, the alterations being mainly connectivity decreases within multiple networks, including language (Waites *et al.* 2006), memory (Bettus *et al.* 2009) and auditory

networks (Zhang *et al.* 2009b) within the temporal lobe, the visual, sensorimotor and dorsal attention networks (Zhang *et al.* 2009b) and the DMN (Zhang *et al.* 2010). Increased connectivity has been shown within the primary visual cortex (Zhang *et al.* 2009b), the DMN (Zhang *et al.* 2010) and the temporal lobe (Bettus *et al.* 2009), possibly reflecting a compensatory mechanism.

There have been few publications on RSN functional connectivity and paediatric epilepsy so far and they have included patients with generalized epilepsy (Bai *et al.* 2011, Killory *et al.* 2011, Pizoli *et al.* 2011), and the results have pointed to both an increase and a decrease in connectivity.

Recent publications have given proof that even MRI data on functional connectivity could provide a useful pre-operative mapping tool, since this method has shown a good correlation with task-based mapping and intra-operative cortical stimulation in brain tumour patients (Zhang *et al.* 2009a). Whether it could be used as a preoperative method for mapping language and memory function in epilepsy patients needs to be investigated further.

3 Aims of the research

The purpose of the present work was to investigate whether children with non-lesional temporal lobe epilepsy with normal intelligence have learning difficulties and whether the learning difficulties that they may have can be investigated using functional magnetic resonance imaging. We were particularly interested in whether functional MRI could reveal alterations in neural networks in children with non-lesional temporal lobe epilepsy. The specific aims were:

1. To assess the extent to which non-lesional paediatric TLE patients have neuropsychological deficits predisposing them to learning difficulties (I),
2. To examine whether the various features of epilepsy affect neuropsychological performance in patients with non-lesional TLE (I),
3. To investigate whether resting-state fMRI findings differ between non-lesional TLE patients and healthy controls (II, III),
4. To study whether the neural response to cognitive tasks differs between non-lesional TLE patients and healthy controls (IV), and
5. To determine whether fMRI findings vary along with EEG findings (II, III, IV).

4 Subjects and methods

4.1 Patients

All the children aged 8–15 who had visited the child neurology clinics at Oulu University Hospital and Länsi-Pohja Central Hospital with a diagnosis of TLE during the years 1996 and 2007 were identified from the medical records. The records of all children with focal epilepsies, covering ICD-10 (1999) diagnosis codes G40.0 to G40.22, were reviewed (N = 247). These hospitals treat all the children with epilepsy resident in their catchment areas. The diagnoses had been reached on the basis of clinical seizure semiology and EEG findings according to the classification of the International League Against Epilepsy (ILAE 1989). Autonomic and/or psychic symptoms, olfactory sensory phenomena and epigastric sensations were considered to represent the amygdalo-hippocampal seizure type according to the ILAE criteria and auditory hallucinations/illusions, dreamy states, visual misperceptions and language disorders to represent the lateral temporal seizure type.

4.1.1 Inclusion and exclusion criteria

The inclusion criteria for the study were age between 8 and 15 years, normal 1.5 T MRI results and a normal intelligence quotient (IQ >85). These children fulfilled our operational definition of "non-lesional TLE", although the possibility of lesions that were not visible on the MRI scan cannot be excluded. Children with interictal EEG abnormalities outside the temporal area were excluded.

4.1.2 Recruitment of patients

The parents of the 32 eligible patients were first sent information about the study and then contacted by telephone. Ten of them did not want to participate and one decided not to continue after the first visit. The ten children did not differ from the participants in terms of demographic data. To ensure that all the mentally retarded children with TLE had been excluded, we performed a further IQ test (Wechsler 1999) on all the participants before their final enrolment. The final number of patients was 21 (Fig. 1).

4.2 Control group

Healthy controls were recruited through three local authority schools representing a normal Finnish child population. A letter providing information on the study was sent to 500 pupils between the ages of 8 and15 years, and 77 of them volunteered to participate (Fig. 1). Children with neurological disorders, psychiatric diagnoses or known learning difficulties were excluded. After matching for gender and age within three months, 39 families were contacted by phone and 21 were finally selected as controls.

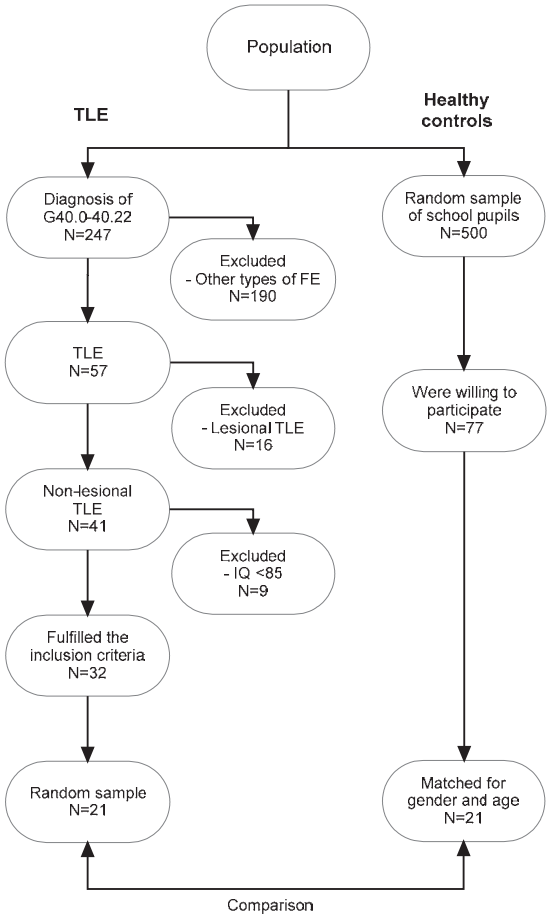

Fig. 1. Recruitment of participants.

4.3 Ethics

The research was approved by the Ethics Committee of Oulu University Hospital, and informed consent was obtained from the child and at least one parent in every case.

4.4 Neurological evaluation

4.4.1 Neurological assessment

The clinical assessment included a medical history and neurological examination performed by the present author. A routine scalp EEG was recorded according to the international 10–10 system and analysed for the presence of epileptiform spikes, spike-waves or sharp waves. The equipment used was a 40-channel NicoltOne EEG system with a sampling frequency of 256 Hz. The recording lasted for 30–45 minutes, and sleep recordings were obtained if feasible, the children having been deprived of sleep. The EEGs were interpreted using bipolar and common average reference montages.

4.4.2 Neuropsychological assessment

The Finnish version of the Wechsler Intelligence Scale for Children – III (Wechsler 1999) was used to assess each child`s intellectual level. The intelligence quotient (IQ) was estimated and the following subtests were analysed separately: Information, Comprehension, Similarities, Arithmetic, Digit Span, Picture Completion, Block Design and Digit Symbol.

The following subtests from the Finnish version of a developmental neuropsychological assessment (NEPSY®, Korkman *et al.* 1998) were administered to all the participants in order to assess their memory and learning functions: Memory for Names (immediate and delayed), Narrative Memory (immediate and delayed), Sentence Repetition and List Learning, Verbal Fluency and Comprehension of Instructions for language function and Design Copying for visuospatial function. Reading was evaluated by means of the Phonological Processing subtest of NEPSY® and a non-standardized reading test evaluating reading speed, fluency and accuracy in which the time taken for each participant to read a story consisting of four sentences aloud was measured in seconds (Lezak

1995). The difficulty of the story was adjusted according to the age of the participant.

4.5 Radiological evaluation

4.5.1 Structural MRI

Imaging was performed using a 1.5 T General Electric Signa HDX 8-channel parallel imaging-coil ASSET system with an acceleration factor of 2.0. Hearing was protected using ear plugs and motion was minimized by means of soft pads fitted over the ears. T1-weighted 3D FSPGR BRAVO sequence images (FOV 24 cm × 24 cm, 256 × 256 matrix, whole brain coverage, flip angle 20°, BW 15.63 kHz, TR 12.4 ms, TE 5.2 ms) were taken in order to obtain anatomical images for co-registration of the fMRI data on standard space coordinates. In addition, T2 FLAIR axial (TE/TI/TR 134/2250/9000 ms, FOV 25.6 cm × 25.6 cm, 288x288 matrix, flip angle 90°) and coronal (TE/TI/TR 124/2000/8002 ms, FOV 25.6 cm × 25.6 cm, 256x224 matrix, flip angle 90°), sequences were imaged for a shortened epilepsy protocol after the fMRI sequences. The T2 coronal scans were replaced with T2 FLAIR in order to reduce scanning time. The anatomical images were inspected by a neuroradiologist, V. Kiviniemi.

4.5.2 Functional MRI

Functional scanning was performed using EPI GRE sequences (FOV 25.6 cm × 25.6 cm, 64 × 64 matrix, flip angle 90°, TR 1800 ms, TE 40 ms) with whole brain coverage in the form of 28 oblique axial 4 mm slices with 0.4 mm spaces between them. The first three images were excluded owing to T1 equilibrium effects.

Resting state

Resting-state scanning lasted for 7 minutes 36 seconds, producing 253 brain volume data sets. The children were asked to lie still during scanning, to stay relaxed and awake and to stare at the cross on the screen.

Task-induced BOLD response

The BOLD response was imaged during the following cognitive tasks: reading single words, memory encoding and retrieval, and listening to a story. There was a 1.5 h break between the memory encoding and retrieval tasks.

Reading task

In the reading task single words derived from two neuropsychological test batteries (Christensen A-L 1977, Korkman *et al.* 1998) were presented on a screen in a block-designed manner and the participants were asked to read each word silently in their minds. Each word was presented for three seconds with a one-second pause in between. Each block included five words, thus lasting for 20 seconds. The subjects were instructed to rest between the task blocks and look at a fixation cross, thus providing a baseline control period lasting for 20 seconds. A total of six task periods with a control period were presented. The whole task lasted 4 minutes.

Memory encoding task

The memory encoding task was similar to the word reading task except that the participants were instructed not only to read the words but also to memorize them. The same words as in the preceding reading task were presented in a block-designed manner with a fixation cross providing a baseline control period, as in the reading task described above.

Story listening task

In the story listening task (Scheef *et al.* 2000, Ahmad *et al.* 2003) the participants listened to a story adapted from a Finnish children's book (Kunnas & Kunnas 1985). This story was evaluated as being appropriate and interesting enough for the age group concerned. It contained 190 words and was read by an adult native Finnish-speaking female speaker. It was presented in a block-designed manner in 30-second listening task periods lasting a total of 4 minutes 15 seconds. During the control periods of 30 seconds each the same recording was played backwards (e.g. "listening" as "gninetsil") in order to keep the acoustic input similar to that during the active condition. The reversed text served as a baseline condition for

regression of the activations in FEAT analysis. The participants were instructed to listen to the story so that they could remember it after the scan, and were also told that the control period text played backwards would sound like gibberish and they should not even try to understand it.

Memory retrieval task

In this task single words were presented on the screen in a block-designed manner. Each block of words lasted for 20 seconds and was followed by a 20-second block with a fixation cross that served as a control condition. The task included 6 blocks of 5 words each. Of all the words used during the task, 15 were taken from the word list the children had memorized during the pause between the scanning sessions. The children were instructed to read each word silently in their minds, and try to recall at the same time whether the word was in the list that they had memorized previously during the pause. If they remembered the word as having been in the list, they were to press a button under their right forefinger. They had been trained in pressing the button in the scanner before the scanning started. The performance data derived from these responses were recorded using the presentation software.

The repetition time was chosen to be relatively short in order to maximize the statistical power of the analyses. The reading, memory encoding and memory retrieval tasks had 135 brain volumes and the story listening task 142 volumes. The first four images were excluded owing to T1 equilibrium effects. T1-weighted 3D FSPGR BRAVO sequence images were taken in order to obtain anatomical images for co-recording of the fMRI data on standard space coordinates. Presentation software (model/version) running on a dedicated pc-computer was used in all the fMRI tasks to synchronize the task with the scanner t-pulses and to monitor the responses in the memory retrieval task. The listening task was presented to the subjects via sound-conducting ear plugs inserted into the ear canals. Secondary ear protectors were used on top of the ear plugs to minimize scanner noise. The words were presented via a DLP data projector (ASK Proximal M2 +) with a retrofitted lens focusing the image onto a translucent screen inside the scanner. The data projector was placed in a secondary Faraday's cage in the scanner room.

4.5.3 Pre-processing of imaging data

The fMRI data were corrected for head motion by multi-resolution rigid-body co-registration of volumes as implemented in the FSL 3.3 MCFLIRT software (Jenkinson *et al.* 2002). The default settings used were: middle volume as reference, three-stage search (8 mm rough + 4 mm initialized with 8 mm results + 4 mm fine grain initialized with the previous 4 mm step results) with final trilinear interpolation of the voxel values and normalized spatial correlation as the optimization cost function. Brain extraction was carried out for motion-corrected BOLD volumes with optimization of the deforming smooth surface model, as implemented in the FSL 3.3 BET software (Smith 2002) using threshold parameters f = 0.5 and g = 0, and using the parameters f = 0.25 and g = 0 for the 3D FSPGR volumes. This procedure was verified by visual inspection of the extraction result. In some cases in which the eye/tonsil tissue was not removed appropriately from the image, these tissues were extracted by manually segmenting them from the image data. The resulting image data were used as a mask for a secondary brain extraction.

In the ReHo analysis the BOLD data were temporally band-pass filtered ($0.01 < f < 0.08$ Hz) by means of the AFNI software (Cox 1996) to reduce physiological noise (Lowe *et al.* 1998, Greicius *et al.* 2003) and to remove any linear trend.

In the dual regression ICA after BET the BOLD volumes were spatially smoothed and 5 mm FWHM Gaussian kernel and voxel time series were detrended using a Gaussian linear high-pass filter with a 100-second cut-off. The FSL 4.1.4 fslmaths-tool was used for these steps. Multi-resolution affine co-registration as implemented in the FSL 4.1.4 FLIRT software (www.fmri.ox.ac.uk) was used to co-register mean non-smoothed fMRI volumes with the 3D FSPGR volumes for the corresponding subjects and 3D FSPGR volumes with the Montreal Neurological Institute (MNI) standard structural space template (MNI152_T1_2mm_brain template included in FSL). Tri-linear interpolation was used, a correlation ratio was used as the optimization cost function, and a search regarding the rotation parameters was performed in the full ($-\pi$ π) range. The resulting transformations and the tri-linear interpolation were used to spatially standardize the smoothed and filtered BOLD volumes to the 4 mm MNI standard space. The 4 mm resolution was retained after spatial normalization, however, for computational reasons pertaining to the later analysis

steps. The quality control of normalization was verified visually with the browser viewer tool from groupPICA MELODIC.

In order to reduce warping-related artifacts and non-matching datasets, we used an existing grey matter 3D template of adolescent subjects with a relatively similar age range (Paakki *et al.* 2010, Rahko *et al.* 2012). This template had been produced earlier from datasets of T1-weighted 3D FSPGR images with FSL-VBM (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html#overview), a voxel-based morphometry style analysis (Ashburner & Friston 2000, Good *et al.* 2001) carried out with FSL tools (Smith *et al.* 2004). This template was co-registered in a standard 2 mm T1 MNI space.

4.6 Statistical methods

Paper I

The group means of the neuropsychological test scores were compared between the TLE group and the control group using the paired t-test. The results of these comparisons are presented as mean differences or with their 95% confidence intervals (95% CI). Multivariate linear regression analysis by the stepwise method was applied to the TLE group to evaluate the relationships between the neuropsychological test results and seizures, interictal EEG, age at onset and duration of epilepsy. The degree of multi-collinearity of each independent variable with the other independent variables was measured using the variance inflation factor (VIF) in the regression model. There was no serious sign of multi-collinearity, because VIF was less than 2.5 for each independent variable. The statistical analyses were performed using IBM SPSS Statistics 19.0.

Paper II

Within-subject analysis was first performed using the ReHo approach. This was done on a voxel-by-voxel basis by calculating Kendall's coefficient of concordance (KCC) (Kendall & Gibbons 1990) for the time series of a given voxel with its 26 neighbouring voxels, as described earlier (Zang *et al.* 2004, Yuan *et al.* 2008).

A larger W value (between 0–1) for a given voxel indicates greater regional coherence within a cluster made up of the voxel and its nearest neighbours. REST

(www.restfmri.net), a Matlab-based resting-state data analysis tool, was used to assess the individual ReHo maps. Each reading was divided by the subject's global mean KCC value within the brain mask (Cao *et al.* 2006, Wu *et al.* 2009). This is a standardization procedure similar to that used in PET studies (Raichle *et al.* 2001). The standardized maps were smoothed using the Gaussian kernel function (FWHM = 4 mm) for better anatomical comparability of the ReHo values at the group level.

To explore the differences between the groups, paired two-sample t-tests (AFNI 3dttests –paired) were performed to create group difference maps for the age and gender-matched pairs. The epilepsy group was divided into subgroups according to the interictal EEG findings at the time of the examination. Subgroups with normal interictal EEGs (EEG-, n = 12) and with interictal EEG abnormalities (EEG+, n = 9) were assessed separately against equal numbers of matched control subjects. The EEG+ subgroup was also analysed by flipping the side of the three right temporal lobe EEG foci to the left side by means of the 3dLRflip–tool in AFNI. Using the AFNI Monte Carlo simulation program AlphaSim (cluster connection radius 3 mm, individual voxel threshold probability 0.01, 1000 iterations), a corrected significance level of $p < 0.05$ was obtained for a minimum volume of 50 voxels (400 mm^3) (Cox 1996) in order to identify significant changes in ReHo. The AFNI program 3dclust was used to obtain cluster sizes, locations and their respective t-values. The probabilistic anatomical atlases included in AFNI were used to help locate the anatomical areas corresponding to the clusters (Eickhoff *et al.* 2007). For presentation purposes, the statistical maps were transformed to Talairach coordinates (Talairach & Tournoux 1988) and superimposed on the higher-resolution anatomical template available in MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html).

Paper III

Group spatial ICA analysis was carried out using FSL 4.1.4 MELODIC software and implementing probabilistic independent component analysis (PICA, Beckmann & Smith 2004). The multisession temporal concatenation tool in MELODIC was used to perform PICA-related pre-processing and data conditioning in a group analysis setting. Spatial ICA using 70 independent components (ICs, high model order) was used to detect the RSNs, as described earlier (Kiviniemi *et al.* 2009, Smith *et al.* 2009, Littow *et al.* 2010, Abou-Elseoud *et al.* 2010). These maps were thresholded using an alternative

hypothesis test based on fitting a Gaussian/gamma mixture model to the distribution of voxel intensities within the spatial maps (Beckmann *et al.* 2005) and controlling both positive and negative false discovery rates at P = 0.5. The RSN sources were separated out by an experienced neuroradiologist, V. Kiviniemi, employed previously described criteria (Kiviniemi *et al.* 2003, Kiviniemi *et al.* 2009).

The between-group analysis of RSN's was carried out using a dual regression technique that allows for voxel-wise comparisons of resting functional connectivity (Filippini *et al.* 2009, Littow *et al.* 2010). This approach identifies subject-specific temporal dynamics and associated spatial maps within each subject's fMRI data set. This involves (A) using the group-ICA spatial maps in a linear model fit against the separate fMRI data sets, resulting in time-course matrices describing the temporal dynamics for each component and subject, and (B) using these time-course matrices to construct subject-specific spatial maps. Finally, the subject-specific dual-regressed component maps for all the subjects were collected into individual 4D files (1 per original ICA map) and tested voxel-wise for statistically significant differences between the groups using non-parametric permutation testing with 500 permutations and the threshold-free cluster enhanced (TFCE) technique (Nichols & Holmes 2002). Differences between the groups were calculated using a $P < 0.05$ corrected for multiple comparisons with the TFCE procedure at the voxel level. In the sub-group analysis each TLE subject was analysed with a matched pair in equal numbers of controls.

The resulting group components were inspected visually and assigned to commonly described RSNs as previously reported (Nichols & Holmes 2002, Kiviniemi *et al.* 2009, Smith *et al.* 2009, Abou-Elseoud *et al.* 2010). The Juelich histological atlas incorporated in FSL and the Harvard-Oxford cortical and subcortical atlases (Harvard Center for Morphometric Analysis) which are provided with the FSL4 software were used to identify the anatomical characteristics of the resulting PICA maps. Only grey matter IC maps with significant differences between the groups are shown in the results. The FSL4 fslstats and fslmaths tools were used to calculate the numbers of non-zero voxels in the selected difference maps and their t-scores.

Paper IV

After obtaining individual-level activation data for the given tasks (i.e. reading, listening, memory encoding and recall), a higher-level analysis was carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 only (i.e., without the final Markov Chain Monte Carlo (MCMC) -based stage (Beckmann *et al.* 2003, Woolrich *et al.* 2004a, Woolrich *et al.* 2004b), and Z (Gaussianized T/F) statistical images were threshold-adjusted using a voxel-level Z-score > 2.3 and a cluster significance threshold of $P < 0.05$ corrected for multiple comparisons (Jenkinson & Smith 2001). In order to estimate the deactivation/activation areas in the groups, a low-threshold z-score of 0.5 was also used with a $P < 0.05$ cluster significance level. FSL4 (Harvard-Oxford, Juelich, MNI) and AFNI (Talairach) atlases were used to recognize the activated anatomical areas. The reading task and story listening task were analysed separately, while the memory encoding and retrieval task data were analysed in conjunction with the reading task data, the initial reading task being used as a regressor to separate reading-related brain activations from memory encoding and retrieval-related activity.

5 Results

5.1 Neuropsychological performance in children with temporal lobe epilepsy having normal MRI findings

The mean IQ was 100 (range 85–135) in the TLE group and 100 (range 85–130) in the healthy control group. The neurological examination and brain MRI results were normal in both groups. The EEG results were normal in all cases in the control group, while the findings in the TLE group are presented in Table 1.

The performance of the TLE group did not differ statistically significantly from that of the healthy control group in any of the subtests. Comparison by gender showed that the girls in the epilepsy group performed significantly less well than those in the healthy control group in the following subtests: Verbal Fluency, Phonological Processing, Delayed Memory of Names, Digit Symbol and Delayed Narrative Memory (Table 2). The boys' performance did not differ between the TLE and the healthy control groups in any of the subtests.

Table 1. EEG characteristics of 21 non-lesional temporal lobe epilepsy patients.

EEG finding	At the onset of epilepsy		At the time of the investigation	
	Girls	Boys	Girls	Boys
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Interictal EEG				
normal	6/11 (55%)	3/10(30%)	7/11 (64%)	5/10 (50 %)
abnormal*	5/11 (45%)	7/10 (70%)	4/11 (36%)	5/10 (50 %)
EEG laterality				
left	1/5 (20%)	2/7 (29%)	1/4 (25%)	4/5 (80%)
right	3/5 (60%)	0/7 (0%)	3/4 (75%)	0/5 (0%)
both	1/5 (20%)	5/7 (71%)	0/4 (0%)	1/5 (20%)

Table 2. Means of neuropsychological test scores, differences of means with 95% confidence intervals (95% CI) and P-values of paired t-tests between the girls and boys with temporal lobe epilepsy (TLE) and healthy controls.

	Girls (N = 11)				Boys (N = 10)			
	TLE	Controls			TLE	Controls		
Neuropsychological test	Mean (SD)	Mean (SD)	Difference (95% CI)	P-value	Mean (SD)	Mean (SD)	Difference (95% CI)	P-value
Verbal Fluency	17.2 (4.7)	23.5 (4.1)	-6.4 (-9.5 to -3.2)	0.001	16.9 (4.9)	16.3 (4.9)	0.6 (-4.8 to 6.0)	0.808
Delayed Memory of names	8.7 (4.3)	12.4 (0.9)	-3.7 (-6.3 to -1.2)	0.009	9.3 (2.9)	9.3 (3.2)	0 (3.1 to 3.1)	1.000
Phonological Processing	9.4 (2.9)	11.2 (2.1)	-1.8 (-3.3 to -0.4)	0.018	9.0 (3.4)	8.2 (2.8)	0.8 (-3.0 to 4.6)	0.646
Digit Symbol	8.6 (2.8)	12.1 (4.0)	-3.5 (-6.7 to -0.2)	0.040	8.1 (3.0)	8.0 (2.9)	0.1 (-2.5 to 2.7)	0.932
Delayed Narrative Memory	10.1 (4.3)	12.9 (1.8)	-2.8 (-5.5 to -0.8)	0.045	9.1 (2.9)	9.8 (2.0)	-0.7 (-3.5 to 2.1)	0.588

5.2 Effects of epilepsy features on neuropsychological performance in patients with non-lesional TLE (I)

Age at onset of epilepsy was significantly associated with performance in two subtests: Digit Span forward (b = 0.37, 95% CI 0.1 to 0.6, P-value 0.006, R Squared 34.0) and Design Copying (b = 0.42, 95% CI 0.05 to 0.79, P-value 0.030, R Squared 22.4).

The duration of epilepsy had a significant negative association with performance in the test measuring Information (b = -0.76, 95% CI -1.5 to -0.03, P-value 0.041, R Squared 20.1) and the Digit Symbol test (b = -0.65, 95% CI -1.2 to -0.07, P-value 0.031, R Squared 22.3).

Interictal EEG abnormalities (N = 9) had a significant negative association with performance in the Delayed Narrative Memory test (b = -3.6, 95% CI -7.1 to -0.08, P-value 0.045, R Squared 19.4).

The presence of seizures did not influence the neuropsychological performance.

5.3 Resting-state fMRI differences between the non-lesional TLE patients and the healthy controls (II, III)

5.3.1 Alterations in the regional homogeneity of baseline brain activity (II)

The synchrony of regional brain activity in resting-state fMRI as analysed by the ReHo method differed significantly between the children with non-lesional TLE and the healthy controls in four brain areas. Increased ReHo was found in the left posterior cingulate gyrus, the right uncus (=anterior parahippocampus) and the right periventricular white matter, while decreased ReHo was found in the left cerebellar culmen (see Paper II, Figure 1).

5.3.2 Alterations in resting-state functional connectivity (III)

The patients with TLE had significant connectivity reductions relative to the controls in four resting-state networks, those represented by the independent components (ICs) nos.11, 23, 47 and 56 (see Paper III, Figure 1). No converse changes implying increased connectivity were detected.

The most significant connectivity reductions were found in IC 11, i.e. in the superior and middle frontal gyri, the inferior temporal gyrus, the precentral gyrus and premotor cortex and the posterior parts of the cingulate gyrus. This brain area comprises the anterior part of the default-mode network.

5.4 BOLD signal differences between the non-lesional TLE patients and the healthy controls during cognitive tasks (IV)

The BOLD signal response differed significantly between the TLE group and the control group in the story listening task requiring auditory comprehension and auditory memory. Significant differences were found in the right hemispheric temporal structures, including the hippocampus, superior temporal gyrus, Heschl`s gyrus and insula and in the thalamus and basal ganglia (see Paper IV, Figure 2).

BOLD response differences were seen in the form of both activation and deactivation differences. The TLE group showed significantly increased activation relative to the control group in the temporal cortical areas and significantly decreased deactivation in the thalamus and the basal ganglia, and to less extent in the temporal areas.

5.5 Differences in fMRI findings in relation to interictal EEG findings between the non-lesional TLE patients and the healthy controls (II, III, IV)

5.5.1 Alterations in the regional homogeneity of baseline brain activity (II)

When the ReHo analysis for the epilepsy group was carried out relative to the EEG findings significant synchronicity alterations were located differently from those identified in the comparison between the whole TLE group and the controls.

The EEG_{pos} patients showed significantly increased homogeneity relative to the controls in the right fusiform gyrus and in the medial part of the left cingulate gyrus. No significant homogeneity decrease was found between the EEG_{pos} patients and the healthy controls (see Paper II, Figure 2).

The EEG_{neg} patients had significantly increased ReHo in the left posterior cingulate gyrus and the left superior temporal gyrus, the right inferior and medial

frontal gyri and the right uncus (=parahippocampus) relative to the controls. Decreased ReHo was detected in the right inferior frontal gyrus (BA 46) and the left cerebellar inferior semilunar lobule (see Paper II, Figure 3).

5.5.2 Resting-state connectivity differences (III)

Connectivity in the EEG_{pos} patients was significantly decreased relative to the controls in four ICs and increased in one IC (see Paper III, Figure 2). Additionally, a significant increase in anti-correlation was found in one IC in the EEG_{pos} patients.

Significantly decreased connectivity was found in ICs 11 and 23 in the EEG_{pos} patients, as in the comparison between the whole TLE group and the controls. In addition, significant connectivity decreases in ICs 63 and 66 were found among the EEG_{pos} patients, the former including areas mainly in the superior parietal lobules (SPL) and the thalamic structures and the latter consisting of cerebellar area VIII. An increase in anti-correlations relative to the controls was found in IC 63, i.e. in the bilateral SPL network, especially in the thalamus and the left temporoparietal (sub)cortical areas. Increased connectivity was found in IC 40, which corresponds anatomically to the dorsolateral visual cortex (V2-4). The increased connectivity found in IC 40 and the increased anti-correlation in IC 63 persisted even when comparison was made separately with the TLE_{neg} patients (see Paper III, Figure 3).

All the significant network disruptions in the EEG_{neg} patients were connectivity reductions relative to the controls (see Paper III, Figure 4). In general, there were less differences in total between the EEG_{neg} group and the controls than between the EEG_{pos} group and the controls. Reduced connectivity was detected in IC 61, comprising the posterior variant DMN, in IC 4, including mainly the precuneus and being closely linked to the posterior DMN, and in IC 55, comprising the executive network.

5.5.3 BOLD response differences during cognitive tasks (IV)

The EEG_{pos} patients showed more extensive BOLD changes bilaterally in the temporal structures, the basal ganglia and the thalamus relative to the controls. In this subgroup all the significant differences took the form of increased activation (see Paper IV, Figure 3).

When the EEG_{neg} subgroup was compared with the controls, significant BOLD response differences were located in the parieto-occipital cortex and the visual cortex in the left hemisphere (see Paper IV, Figure 3). These took the form of both decreased activation and increased deactivation in the EEG_{neg} patients relative to the controls.

6 Discussion

6.1 Neuropsychological performance in children with temporal lobe epilepsy having normal MRI findings

The main finding to emerge from this work was that the patients with well-controlled non-lesional TLE showed good neuropsychological performance on average. The results are not at all as pessimistic as those arising from studies of uncontrolled epilepsy or lesional/symptomatic epilepsy, and we consider them to be highly important in the context of informing parents about their child's epilepsy.

The results showed that a quarter of the children with non-lesional TLE performed quite well in neuropsychological tests and had only a slight tendency for poorer performance in the Verbal Fluency, Delayed Narrative Memory and Immediate and Delayed Memory of Names subtests as compared with the healthy controls (see Paper I, Table 3), although the girls with TLE showed significantly poorer performance than their controls in five subtests affecting memory, language and visuospatial skills. This is in accordance with a recent paper showing that females with childhood-onset TLE had poorer performance in both verbal and non-verbal tests throughout adulthood, suggesting a different inherent vulnerability to TLE in females (Baxendale *et al.* 2010). One possible explanation may lie in the female hormones, which are known to alter the excitability of the central nervous system (Morrell 1999). The reason why the healthy girls in our control group performed better than the healthy boys is unknown. The selection criteria were same for all the healthy schoolchildren, but it is possible that the genders participated in the study in a selective manner. The finding of a gender difference should therefore be interpreted as a preliminary result, since gender differences in cognitive performance in the WISC subtests have not previously been documented. Our sample size was small, however, and the finding should be confirmed in larger studies.

The neuropsychological findings are nevertheless supported by the fMRI results, which show alterations not only in the temporal lobes but also in the networks extending to frontal as well as parietal areas.

When the impact of various epilepsy features was evaluated, early onset and duration of epilepsy were found to have a significant negative effect on neuropsychological performance in subtests requiring visuospatial skills,

psychomotor speed and working memory. Abnormal interictal EEG was found to affect only one subtest requiring verbal memory, and seizures did not influence the neuropsychological performance at all. The seizure frequency in our epilepsy patients was in fact relatively low; about half of the children had had one to three seizures during the previous year while the remainder had been seizure-free.

The mean duration of epilepsy in our series was only 2.5 (range 0.3–8.0) years. Oostrom *et al.* (2003) found impairments in academic skills but not in IQ during the first year after the onset of epilepsy in a series including children with different types of new-onset idiopathic or cryptogenic epilepsy having good seizure control. There are reports suggesting that academic problems may be detected even before the onset of epilepsy (Hermann *et al.* 2007). In the present work a wide range of neuropsychological deficits were found at an early stage of epilepsy, particularly in patients with early-onset epilepsy, and most especially among girls. These results may indicate that in some cases epilepsy affects brain function soon after its perceived onset, while in others the pathophysiological process is quite different from the very beginning.

The prevalence of non-lesional TLE in children with a normal IQ at the age of 8–15 years was found in this population-based study to be 0.7/1000. We could not find any previously reported prevalence figures for this type of epilepsy, but calculating from a previous Finnish report (Eriksson *et al.* 1997), the prevalence of all focal epilepsies among children aged 6–15 years would be 2.3/1000. TLE constitutes about one-third of all focal epilepsies (Loiseau *et al.* 1991, Panayiotopoulos 2007, Sillanpää *et al.* 1999), and our finding is in agreement with this conclusion.

We excluded patients with a lesional aetiology, since we wanted to focus on a less well studied subset of TLE that is in fact more common in paediatric clinical work. Our sample is small and it is possible that more differences would have been detected if it had been larger.

6.2 Alterations in the regional homogeneity of baseline brain activity in paediatric non-lesional TLE (II)

Four areas of altered regional homogeneity in BOLD signals were detected in the children with non-lesional TLE during the interictal state. Importantly, the increased signal homogeneity was seen to occur over a relatively long period of time, since the functional MRI scans lasted 7.5 min. One of the areas of increased ReHo was found in the right temporal lobe. Intracortical EEG measurements have

also shown increased regional synchrony of electrophysiological signals during mesial temporal lobe seizures (Ponten *et al.* 2007). Our findings show that increased synchronization in the temporal lobe can also be detected using the spatially accurate and non-invasive BOLD technique, even in the interictal phase.

Another significantly increased ReHo area in the TLE patients was found in the left medio-posterior part of the cingulate gyrus, the change in the upper posterior cingulate cortex being especially obvious. The posterior cingulate cortex of patients with TLE has also been shown to exhibit significant temporal BOLD signal peaks in 2-dimensional temporal cluster analysis (Morgan *et al.* 2007). Interestingly, our finding falls between the two regions of spike-related BOLD activation and deactivation observed in the cingulate cortex of adult patients with generalized epilepsy (Gotman *et al.* 2005). In particular, the area of deactivation posterior to the corpus callosum as identified by Gotman *et al.* (2005) was close to the area of increased regional homogeneity observed here.

The cerebellar culmen showed decreased ReHo in the epilepsy group relative to the control group. Gotman *et al.* (2005) found strong positive activation correlating with spike-wave EEG patterns in exactly the same area in the frontal mid-line cerebellum in their combined EEG-fMRI study of patients with generalized epilepsy, and most importantly, the source of these changes was strongly coherent EEG activity. As cerebellar function is related to fine motor control, it is plausible that the reduced homogeneity could be a sign of counterbalancing activity aimed at controlling motion. All the patients were seizure-free during the scanning, however, and no motor activity was detected. It has been shown in SPECT studies that patients with focal epilepsy have ictal hyperperfusion in the cerebellum contralaterally to the seizure focus (Bohnen *et al.* 1998, Dupont *et al.* 2009) and bilateral cerebellar hypoperfusion interictally (Van Paesschen *et al.* 2003). Interictal hypoperfusion has been seen not only in the epileptogenic zone but also in anatomically remote areas relative to the epileptogenic focus, including the cerebellum (Van Paesschen *et al.* 2007). This phenomenon, called crossed cerebellar diaschisis, has been thought to indicate disconnection of the glutamatergic corticopontocerebellar tracts (Mewasingh *et al.* 2002, Nelissen *et al.* 2006). These observations, taken together with the results of recent studies of small-world networks (see below), suggest that epilepsy is a disease of the neural networks (Spencer 2002).

The organization of the human brain cortex has recently been characterized as a scale-free small-world network (van den Heuvel *et al.* 2008, He *et al.* 2009). In scale-free networks local sub-networks are closely interconnected by a

relatively small number of hub voxels (van den Heuvel 2008), and these 'connector hubs' have a central role in the pathophysiology of various brain diseases (Netoff *et al.* 2004, Achard *et al.* 2006, Reijneveld *et al.* 2007, Morgan & Soltesz 2008). As epileptic activity spreads in the brain it alters the network topology towards more ordered signalling with more pronounced clustering and greater path lengths (Ponten *et al.* 2007).

The results obtained here show that epilepsy alters local signal synchrony at the sub-network level in the long term. Regional homogeneity represents the regional connectivity of the brain tissue and may be seen as a measure of the smallest network integrity measurable by fMRI techniques. It can be hypothesized that in the areas of altered homogeneity the hubs may have an abnormal synchrony signal, inducing the spread of epileptiform activity across the brain network boundaries. Further network topology investigations may reveal interesting alterations in cases of epilepsy.

Interestingly, decreased ReHo signals were found in the left inferior semilunar lobule and the right inferior frontal gyrus of the patients with normal EEGs, whereas findings of increased ReHo, especially in the right hemisphere, were more prominent in this group of patients than in those with abnormal EEGs.

ReHo analysis has been shown to identify white matter alterations in other diseases as well (Paakki *et al.* 2010). Our finding of increased ReHo in the right periventricular white matter is difficult to explain, as the BOLD signal should not receive much of a contribution from the relatively less perfused white matter. However, there have been an increasing number of preliminary findings of time domain susceptibility-weighted signal alterations, including BOLD, in white matter (Kiviniemi *et al.* 2009, Mezer *et al.* 2009), and this aspect warrants further research.

Data-driven analysis of ReHo for the detection of epileptiform abnormalities avoids the problems attached to the timing of the often absent interictal activity and utilizes epilepsy-related alterations in synchrony to reveal epileptic abnormality. This is in accordance with the fact that the BOLD signal changes precede the EEG changes in focal areas (Makiranta *et al.* 2005, Jacobs *et al.* 2009). Even though the EEG and BOLD signals are sampled on different spatial and temporal scales, it seems that epileptiform activity increases regional synchrony on several temporal scales that are also detectable by way of BOLD signals. The present findings suggest that the synchrony alterations observed in epilepsy are not only related to seizure onset but seem to extend to long-term

regional synchrony as well (Ponten *et al.* 2007). This is particularly interesting, since half of our epilepsy patients had normal interictal EEGs.

All our patients were receiving antiepileptic medication. To our knowledge, studies on the effect of AEDs on BOLD signals in humans have been performed only with valproate (Bell *et al.* 2005) and midazolam (Kiviniemi *et al.* 2005, Greisius *et al.* 2008). Valproate was shown to reduce the BOLD signal response to a stimulus and midazolam to reduce functional connectivity, probably due to the decline in blood flow at a Ramsey score 3 sedation level, where the subject responds only to strong external commands. Further studies on the effects of AEDs on functional connectivity measures such as ReHo are needed to differentiate between the effect of medication and disease-related alterations. The eradication of AED effects from epileptic patient data requires international collaboration efforts, and such international database studies are indeed being planned in the field of resting-state brain connectome research (http://www.nitrc.org/projects/fcon_1000/).

Our results emphasize the importance of ReHo analysis as a new data-driven tool for the detection of interictal epileptiform abnormality, and possibly as an additional non-invasive tool for detecting epileptogenic foci. They also strengthen the idea that alterations in synchronization have a central role in epileptogenesis. On the other hand, one might also argue that, due to the shortcomings of EEG, one may not be able to detect certain aspects of abnormal epileptic activity. In addition, the causal links between EEG and BOLD signals may not be understood well enough at the moment (Laufs *et al.* 2008).

6.3 Functional connectivity disruptions within resting-state networks in children with non-lesional TLE (III)

Functional connectivity in several resting-state networks was significantly reduced in the TLE patients relative to healthy controls. These connectivity alterations seemed to occur in different networks depending on the presence or absence of interictal epileptiform activity, and they were clearer and more robust in the subgroup of patients with abnormal EEGs, with two additional significant features: increased connectivity and anti-correlation.

The EEG_{pos} subgroup predominated, with reduced functional connectivity in the frontal brain regions, especially in IC 11, corresponding to the ventromedial prefrontal variant of the DMN (Kiviniemi *et al.* 2009). By contrast, the EEG_{neg} subgroup showed the clearest connectivity reductions in the posterior parts of the

DMN and in IC 4, which is closely linked to the posterior DMN. Frontal connectivity reductions were seen to a lesser extent in the EEG_{neg} subgroup, and reduced connectivity was also found in the executive-type network, but not in the DMN as was the case in the EEG_{pos} subgroup. The decreased connectivity in the anterior parts of the cerebrum is well in line with previous findings in DMN and adult TLE patients (Liao *et al.* 2010, Zhang *et al.* 2010).

Reduced connectivity within the primary visual RSN (IC 23), has not been reported earlier. It was found in the TLE patients when analysed as a single group, but when the analysis was carried out separately in relation to the EEG findings the reduction seemed to be attributable to the patients with abnormal EEGs. The reduction site within the primary visual network was located in the superior parietal lobule, while the primary visual cortex itself remained intact. Interestingly, we found significantly decreased parietal connectivity in the SPL network, and this was likewise seen only in the EEG_{pos} subgroup. The site of the decreased connectivity is in line with one previous observation in adult TLE patients, where connectivity reduction occurred in the higher order visual area, which is known to be engaged in the processing of visual motion detection, whereas connectivity was increased in the primary visual area (Zhang *et al.* 2009b).

Psycho-behavioural studies have reported that the primary visual function is not impaired in TLE (Grant *et al.* 2008, Vannucci *et al.* 2003). Instead, the problem seems to lie in impaired perceptual networks (Erickson *et al.* 2006). Behavioural studies have also shown that interictal somatosensory and tactile processing is impaired in TLE patients (Beckung *et al.* 1993, Knecht *et al.* 1996, Grant *et al.* 2005). Notably, simple focal seizures in TLE can occur as perceptual illusions or hallucinations in all sensory modalities and can be preceded by somatosensory auras. Our findings of parietal connectivity disruptions in various resting-state networks and of abnormal anti-correlations in the thalamus in relation to SPL network activity are thus in agreement with previous observations. Interestingly, the SPL network falls within the posterior parts of the somatosensory cortex, which is considered to play a key role not only in spatial cognition, i.e. in our ability to process and integrate multisensory spatial information acquired from the environment (Sack *et al.* 2009), but also in the analysis of mentally constructed inner mental images (spatial imagery) (Sack *et al.* 2005, Formisano *et al*, 2002).

Increased connectivity was detected only in the patients with abnormal EEGs, where it was found within the dorsolateral (V2-V4) visual RSN (IC 40) in the

form of an abnormal connection with the frontal areas, while connectivity in the dorsolateral visual cortex itself was normal. In a previous connectivity study of adult TLE patients an increase in connectivity was interpreted as reflecting enhanced functionality, as a contra-lateral increase in hippocampal connectivity had a positive correlation with memory scores in neuropsychological tests (Bettus *et al.* 2009). In another adult TLE connectivity study increased connectivity was detected in the posterior cingulate cortex (PCC) among patients who had decreased hippocampal connectivity (Zhang *et al.* 2010). Since the latter was related to the duration of epilepsy, the increased connectivity in the PCC in the same patients was thought to be a sign of a compensatory mechanism. Our finding agrees with the idea of increased connectivity being indicative of a compensatory mechanism, since it was found only in the EEG_{pos} subgroup.

The anti-correlations with respect to the supraparietal lobule (SPL) network detected in the thalamic and subcortical temporoparietal structures in the EEG_{pos} subgroup only are unique to this study and are of special interest since a significant difference in anti-correlation was found relative to both the control group and the EEG_{neg} subgroup. The thalamus is considered to be a central structure in epileptogenesis, being active via thalamo-cortical loop abnormalities (Destexhe 2008). Most of our data on the thalamus and epileptogenesis are derived from animal models with generalized spike and wave discharges or from EEG-fMRI studies in humans with different types of generalized epilepsy (Gotman *et al.* 2005, Badawy *et al.* 2009), and very little is known about how the thalamic networks act in TLE. We suggest, however, that our finding of increased anti-correlation within the SPL network in the thalamic region may be important with regard to epileptogenesis. It could be related to poor epileptic control, which is detectable as an abnormal interictal EEG and altered functional connectivity in fMRI. Use of the simultaneous EEG- fMRI scanning technique would have given more information on anti-correlations, as also on the other connectivity differences between the EEG_{pos} and EEG_{neg} subgroups.

Previous simultaneous EEG-fMRI studies have provided evidence that interictal spike and wave discharges lead to deactivation in the frontal and parietal DMN areas (when measured in terms of BOLD signal intensity). This has been shown both in focal (Laufs *et al.* 2007, Kobayashi *et al.* 2006, Liao *et al.* 2010, Morgan *et al.* 2008) and in generalized epilepsies (Archer *et al.* 2003, Kobayashi *et al.* 2006, Gotman *et al.* 2005). Even though the techniques and measures used differ between BOLD and functional connectivity studies, it is interesting that the results are similar: either deactivation or reduced connectivity is found in the

DMN areas. Both phenomena could indicate that epileptogenic activity has a widespread suspending effect on the baseline state of the brain. However, since the neurophysiological details of changes related to functional connectivity are unknown, one can only speculate as to whether the increased thalamic anti-correlations are a consequence of abnormal inhibitory and/or excitatory mechanisms at the neuronal level. Functional connectivity changes may be either due to reorganization or network impairment or else indicative of a compensatory mechanism.

We found significant RSN connectivity disruptions in the present paediatric non-lesional TLE patients that seemed to be clearly different depending on the interictal EEG findings. Taking the patients as a single group, all the alterations were connectivity decreases, but when the EEG_{pos} subgroup was considered separately this showed a connectivity increase and abnormally anti-correlated activity between the thalamus and the SPL network relative to both the controls and the EEG_{neg} subgroup.

We believe that our findings of altered connectivity in the non-lesional TLE patients could be a mark of functional reorganization in the brain that is dependent on the status of the epileptiform activity seen in the interictal EEG. The connectivity impairments could also be a consequence of the epileptic process preventing normal network development, or even of an inborn defect leading to the manifestation of epilepsy, so that these theories would need further investigation.

6.4 Reading, listening and memory-related brain activity in children with early-stage non-lesional temporal lobe epilepsy - an fMRI study (IV)

Children with non-lesional TLE had a significantly different BOLD response from the healthy controls when listening to a story, whereas the response to tasks requiring the reading, encoding and retrieval of written words was surprisingly similar in the two groups. The majority of the significant differences between the groups when listening to the story were located in the temporal lobes, and we also expected to find BOLD response differences there during the silent reading and memory tasks, since these functions similarly require temporal lobe involvement. Listening to the story was nevertheless the only task that included semantic information, which evidently made it more demanding, a fact that may perhaps

explain the lack of significant differences between the groups during the other tasks.

When the TLE group as a whole was compared with the controls, significant differences in the results of the story task were located in the right hippocampus, STG, Heschl gyrus, insula, thalamus and basal ganglia. Significant differences were seen in both the activation and deactivation patterns, activation being significantly increased and deactivation significantly decreased in the TLE group relative to the controls.

The BOLD response differences were even more extensive when the EEG_{pos} subgroup rather than the TLE group as a whole was compared with the healthy controls, and were seen bilaterally in the temporal structures, thalamus, putamen and pallidum. The significant differences took the form of increased activation in the EEG_{pos} group, arguably reflecting the increased metabolic demand occasioned by the epileptiform activity. It should be noted that there is a continuum of activity increase in the midline basal ganglia regions from the control group to the EEG_{neg} group and finally the EEG_{pos} group, which showed the highest level of activity.

The role of the thalamus is interesting. Traditionally it has been considered to be a central structure in epileptogenesis, being active via thalamo-cortical loop abnormalities, the data concerned being mostly based on animal models with generalized spike and wave discharges (Destexhe 2008, Badawy RA *et al.* 2009) or on EEG-fMRI studies of humans with different types of generalized epilepsy (Gotman *et al.* 2005). In addition, structural MRI studies have reported lower baseline thalamic volumes in adult TLE (Tuchscherer *et al.* 2010) and even developmental trajectory changes in children with new onset epilepsy (Tosun *et al.* 2011, Pulsipher *et al.* 2011). This literature has linked the baseline and developmental volumetric differences with cognitive impairment, particularly in the executive function. Little is known, however, about how the thalamic networks act in TLE. Our present results pointing to an increased BOLD response in the thalamus, together with our previous results suggesting disrupted resting-state connectivity within the thalamic region among TLE patients (Mankinen *et al.* 2012), indicate that the thalamus may also play a key role in TLE.

The interpretation of the negative BOLD response has been controversial (Moraschi *et al.* 2012). We regarded deactivation as a decrease in signal intensity during the target period, as contrasted with either low-attention cross fixation or an inverse situation in the listening task. In general, deactivation was detected in areas both close to and far removed from the activated areas, often affecting

default mode areas, as it should. Deactivation was significantly decreased in the TLE group relative to the controls when listening to the story, and the subgroup analyses at a low Z-score threshold suggest that the EEG_{neg} subgroup showed significantly increased deactivation relative to the controls and the EEG_{pos} subgroup. This could suggest that deactivation is not only a sign of haemodynamic redistribution but may also reflect neuronal inhibition (Stefanovic *et al.* 2005), which is particularly strong in patients with normal interictal EEG. When the inhibitory mechanisms break down and/or are overtaken by the epileptiform discharges and excitation, a positive BOLD response becomes detectable in the thalamocortical networks and is also detected as an abnormal interictal EEG. It is important to note here, however, that the inverse "gninetsil" contrast may automatically catch the child`s attention, even though the children were told to focus on the normal speech. Thus the deactivation seen when listening to the story may be partially due in actual fact to increased activation during the inverse talk as compared with the normal level. The source of the deactivation could have been distinguished by using an additional non-auditive contrast such as a period of scanner noise during the task, but this was not included due to time restrictions in the already quite lengthy scanning session.

The present results demonstrate that it is possible to conduct a paediatric fMRI study with multiple tasks successfully when the children are carefully instructed and trained beforehand. This was demonstrated in two ways. First of all, the activation patterns occurred in similar brain regions to those recorded in previous paediatric fMRI studies of the functional organization of reading (Lee *et al.* 1999, Gaillard *et al.* 2001a, Gaillard *et al.* 2003a, Turkeltaub *et al.* 2003), auditory comprehension (Ulualp *et al.* 1998, Balsamo *et al.* 2002, Ahmad et al 2003) and episodic memory encoding (Menon *et al.* 2005, Chiu *et al.* 2006, Maril *et al.* 2010). This implies that our participants were able to follow the instructions properly and could successfully engage their brain networks in the tasks. The second proof of successful scanning was that all the children who participated were able to complete the scanning without problems.

7 Conclusions

1. Although the patients with non-lesional TLE showed good neuropsychological performance on average, the girls were found to have significant problems in several neuropsychological tests. Of the various epilepsy features, early onset and duration of epilepsy had a significant negative effect on neuropsychological performance, whereas abnormalities in EEG affected only one subtest, that requiring verbal memory, and seizures did not have any impact on neuropsychological performance at all.

   The deficits were not restricted to elements of neuropsychological performance involving the classical temporal lobe memory system, as significant problems were also found in tests requiring frontal and parietal lobe functioning, implying that TLE has to be regarded as a wider brain network disorder affecting brain areas beyond the temporal lobes.

   The neuropsychological findings are supported by the fMRI results, which show alterations not only in the temporal lobes but also in the networks extending to the frontal and parietal areas. Therefore children with early-onset epilepsy, and girls in particular, should be assessed carefully for neuropsychological impairment using sufficiently broad batteries of tests in order to detect even slight deficits.
2. Resting-state fMRI findings differed significantly between the non-lesional temporal lobe epilepsy patients and the healthy controls. Significant differences between the groups were found in terms of both the resting-state regional homogeneity of the BOLD signal and resting-state functional connectivity. The location of the significant differences among the TLE patients seemed to be clearly different depending on the interictal EEG findings. Both the resting state ReHo differences and the RSN connectivity disruptions were detected in the temporal lobes as well as in extensive brain areas reaching outside the temporal lobes, suggesting that TLE should be regarded as a widespread disruption of brain networks and not just malfunction/pathology of a single brain region within the networks. This needs to be taken into consideration when evaluating patients with TLE and their learning abilities, even at an early stage in epilepsy.
3. The BOLD response in a task requiring auditory comprehension and auditory memory was found to differ between the TLE patients and the healthy controls. Activation was found to be significantly stronger in the TLE patients, and in particular among the patients with abnormal EEGs, reflecting

the enhanced metabolic demand caused by the epileptiform activity. Patients with normal EEGs showed significantly stronger deactivation, which may be a sign of neuronal inhibition. This implies that not only activation but also deactivation may have a role in functional brain organization, and both should be imaged when conducting fMRI studies.

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I Mankinen K, Harila M, Rytky S, Pokka T & Rantala H (2013) Neuropsychological performance in children with temporal lobe epilepsy having normal MRI findings. Eur Jour Ped Neurol. In press. DOI http://dx.doi.org/10.1016/j.ejpn.2013.08.005

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