

Epilepsy Research Priorities in Europe

On Behalf of Epilepsy Advocacy Europe

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Summary

The European Forum on Epilepsy Research (ERF2013) took place in Dublin from the 26th – 29th May 2013. It was designed to provide a platform on how to improve the lives of persons with epilepsy in Europe by influencing the future political agenda of the EU. The forum's focus was to listen to the researchers and citizens of Europe involved in epilepsy-related issues either as patients or as healthcare providers. As an output, the ERF2013 defined objectives and milestones for the epilepsy community (1) how to strengthen epilepsy research, (2) how to reduce the treatment gap, and (3) how to reduce the burden and stigma of epilepsy.

Background

The European Forum on Epilepsy Research (ERF2013) was an initiative of Epilepsy Advocacy Europe (EAE), a collaborative joint task force of the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) (<http://epilepsyadvocacyeurope.org>). The Forum was co-funded by the European Commission's 7th Framework Programme and hosted in conjunction with the Irish Presidency of the Council of the European Union during the European Month of the Brain. A total of 270 participants from 57 countries, including each of the 27 EU Member States, were present at the Forum. The ERF2013 elaborated further the contents of the Written Declaration on Epilepsy, which had been approved by the European Parliament in 2011 with a large majority of votes (<http://www.europarl.europa.eu/sides> Baulac et al., 2012).

The main focus of the Forum had three concepts, each separate but inextricably intertwined. Firstly, possibilities were explored as to how the stigma and social burden associated with epilepsy could be reduced through targeted initiatives at EU, national and regional levels. Secondly, there was a specific focus on access to optimal standards of care, as well as discussion surrounding the appropriate response to epilepsy care in Europe. Thirdly, a clear message was delivered to politicians and policy makers that there is a need for further funding in epilepsy research within *Horizon 2020*. The topics specifically discussed, as those requiring extra resources, were:

- Epilepsy in the Developing Brain
- New Targets for Innovative Diagnostics and Treatment of Epilepsy
- What is required for Prevention and Cure of Epilepsy?
- Epilepsy and Co-morbidities – Special Focus on Ageing and Mental Health

Stigma and Burden of Epilepsy

People with hidden disabilities such as epilepsy are among the most vulnerable in any society. From early civilization, epilepsy has been associated with many misconceptions, causing blame and discrimination to individual patients and often to their families as well. A reason for this is that epileptic seizures are sudden happenings with often unusual behavioral and physical symptoms and convulsions.

The stigmatizing nature of epilepsy and its associated psychopathology in people with epilepsy has been well established. In a study involving more than 6,000 adults from 10 European countries, more than half felt stigmatised, and 18% felt highly stigmatised because of their epilepsy [Baker 2000]. Factors predictive of stigma, which varied amongst countries and cultures, included seizure frequency, duration of epilepsy, seizure type and knowledge of epilepsy [Baker 2002].

The global burden of epilepsy includes physical hazards resulting from the unpredictability of seizures, social exclusion as a result of negative attitudes of others toward people with epilepsy and stigma. Children with epilepsy may be banned from school, adults may be barred from marriage, and employment is often denied, even when seizures would not render the work unsuitable or unsafe [de Boer *et al.* 2008]. Up until 1970, for example, there were restrictions on people with epilepsy getting married in the UK, one of the most modern societies in Europe. Much has improved in the past forty years, as evidenced by research in 2004 which shows that public attitudes to epilepsy have improved significantly (Jacoby *et al* 2004). Unfortunately, two recent surveys in 2013 indicate that, in some areas at least, this improvement may have slipped back (Cleaver 2013; Epilepsy Ireland 2013).

Due to continuing concerns over the attitude of peers to seizures, many people still hide their epilepsy from friends, colleagues and fellow students. The hidden nature of the condition, and the sense of difference that persons with epilepsy experience from others

when they have a seizure in public, leads to fears of exclusion from education, employment and social life.

Table 1. Epilepsy facts in Europe.

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- 6 million people with epilepsy in Europe¹
 - Epilepsy is not a single disease but includes hundreds of causes and several different syndromes
 - About 400,000 new cases each year, i.e., 1 new case every minute
 - 100,000 children and adolescents diagnosed with epilepsy each year¹
 - 130,000 people ≥ 65 y of age diagnosed each year¹
 - About 50% of patients with epilepsy feel stigmatized²
 - The death rate in people with epilepsy is 2-3 times higher than that of the general population^{3,6}
 - Life expectancy reduced by 2-10 years^{3,6}
 - Patients with epilepsy have 4-fold risk of co-morbidities that reduce quality of life⁵
 - 15% are difficult to treat and 25% are refractory to current treatments⁴
 - No therapies to prevent or cure epilepsy
 - No biomarkers to identify patients at risk for epilepsy
 - Total cost of epilepsy €20 billion per year⁷
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1. Forsgren L et al. (2005)

2. De Boer H et al. (2008)

3. Hitiris et al. (2007)

4. Brodie M et al. (2012)

5. Kerr MP (2012) .

6. Tomson T et al. (2005)

7. <http://www.ibe-epilepsy.org/downloads/EURO%20Report%20160510.pdf>

The total European population is 729 M (< 15 yr: 137 M; > 65 129 M; Source: Eurostat.Eu). Numbers are rounded.

Need for awareness

Increasing public awareness of what epilepsy is will inevitably improve the quality of life for people with the condition. Increased public support for necessary research to improve treatments for epilepsy and better working, educational and social environments for people with epilepsy will all follow from this. The public also needs to know that epilepsy is a life threatening condition and to be aware of the realities around sudden unexpected death in an individual with epilepsy (SUDEP) and status epilepticus. Many

people view epilepsy as a benign condition and, as a consequence, do not appreciate the need for resources in treatment and research to be directed towards it.

Changing perceptions

For many people with epilepsy, the greatest problems they face are due to stigma, which is caused by the lack of public awareness about the condition (Jacoby et al 2004). The Institute of Medicine's epilepsy report, published earlier this year, says that "Targeted educational programmes and counselling for people with epilepsy and their families are clearly indicated, but this is not enough (<http://www.iom.edu/Reports/2012/Epilepsy-Across-the-Spectrum.aspx>). Initiatives are also required that focus on changing negative public attitudes" (England et al 2013). As the stigma associated with epilepsy can cause more distress than the condition itself, one of the main objectives of all epilepsy organisations is to raise public awareness and knowledge. They also seek to inform politicians and policymakers about epilepsy. Getting good information on prevalence and cost of epilepsy, as well as on epilepsy mortality, will substantially raise the profile of epilepsy. This data will also point to where savings can be achieved by improved diagnosis and treatment.

Publicising

Through the awareness work of IBE organisations in many European countries, conditions have improved dramatically as compared to the situation 30/40 years ago in Europe (Jacoby et al 2004). This has been achieved on tiny budgets in individual countries. Trans-European awareness campaigns could make a huge impact in a short space of time and for a relatively small cost.

Legislation

Well-crafted legislation, which is based on internationally accepted human rights standards, can prevent violations and discrimination; promote and protect human rights; enhance the autonomy and liberty of people with epilepsy; and improve equity in access to health care services and community integration. It is known, however, that in many countries, laws impacting on the lives of people with epilepsy are outdated, failing to adequately promote and protect their human rights and, in some cases, actively violating

those rights. In yet other countries, there is a total absence of legislation in this area. The most recent example of this is in relation to the EC Directive on Driving ([Commission Directive 2009/113/EC](#)), which should have been in place and operating in every EU country by 2010. The right to drive is one of the most important components of quality of life, but, this right is still being denied to many people with epilepsy in EU countries who meet the criteria to obtain a licence as outlined in the EC Directive on Driving.

Despite this knowledge, no comprehensive study has been undertaken to determine the presence or absence, effectiveness or ineffectiveness of legislation to promote and protect the rights of people with epilepsy in Europe ([Pahl and de Boer, 2005](#)). It was for this reason that IBE and ILAE, within the framework of the ILAE/IBE/WHO Global Campaign Against Epilepsy, set up a project on "epilepsy and legislation". As a result of this project, a comparative analysis of epilepsy-related legislation, in over 50 countries worldwide, was conducted under the banner of the Global Campaign. The analysis revealed that many laws fail to meet today's international human rights standards in relation to people with epilepsy <http://www.globalcampaignagainstepilepsy.org/epilepsy-and-legislation/> ([is there a reference or web page](#)).

Standards of Care

Epilepsy is one of the most frequently occurring neurological diseases. It is characterized by its symptoms, the epileptic seizures, which are caused by a variety of different alterations in the brain. Therefore, epilepsy can be viewed as a large group of diseases, summarized by its leading symptom: the epileptic event. The aetiology of the epilepsies ranges from genetic alterations influencing the excitability of the brain, to structural alterations such as developmental disturbances of the cortex, or the consequences of traumatic, inflammatory, or neoplastic and vascular abnormalities of brain tissue. Because of this, the care of a patient suffering from epilepsy – which means a patient suffering from repeated seizures – includes a complex neurological diagnostic program with a high degree of expertise and, in many cases, complex and specialized treatment. Therefore, specialized hands are needed.

Diagnosis and treatment have two facets: firstly, the symptom-oriented treatment deals with the seizure type and its optimal therapy. Secondly, the aetiology of the epilepsy may give rise to a treatment of the cause. The latter is sometimes difficult to find. However,

it has considerable consequences for prognosis and possible alternatives in treatment and should therefore be followed-up carefully. Since all three elements (seizure semiology, EEG and MRI) are very specialized for the epilepsies, the standards of care should be based on a network of medical doctors and/or organizations leading to a stepwise increase in the procedure quality in order to have a balanced relationship between the costs and possible benefits for the patient ([Fitzsimons et al., 2012](#)).

Access to specialist after the first seizure

The first step for patients who have suffered from their first seizure should be a visit to a neurologist or a paediatric neurologist who is involved in the basic diagnostic work-up and, if necessary, prescribes the first anti-seizure medication.

Access to epilepsy specialist for difficult-to-treat patients

Over the years, differentiation develops between those patients who are easy-to-treat with no further consequences and those patients who are difficult-to-treat with possible further consequences concerning diagnosis and treatment. The latter group of patients should be examined by neuro-paediatric and neurological colleagues specialized in epilepsy and/or epilepsy centres.

Access to medical centres specialized to epilepsy

If it transpires that their treatment is not successful within the first five years, then highly specialized centres should take over and confirm the diagnosis, formulate a syndromic diagnosis, and outline the therapeutic options that are still available.

The point prevalence of epilepsy is approximately 0.7% of the population, and up to 40% of individuals with epilepsy are difficult to treat (half of them being refractory to current drugs). Ideally, one highly specialized centre should exist for a population of one to two million people. This would mean that each centre would be responsible for at least 2,000 - 4,000 patients with difficult-to-treat epilepsy and/or the differential diagnosis of seizure-like events. A prerequisite for these centres must be the access to high-resolution MRI, while also having an advanced knowledge of the MRI findings in patients with epilepsy. In addition, in-patient video-EEG long-term recordings of epilepsy patients must be available. The possibility of recording from implanted electrodes (invasive EEG) should also

be available. In addition to the neurological specialists, specialized psychologists (neuropsychologists) and psychiatrists with knowledge of psychiatric symptoms in epilepsy must be members of a specialist multi-disciplinary treatment team. These centres should offer all types of epilepsy treatment: differential pharmaco-therapy, resective epilepsy surgery, stimulation techniques, and the ketogenic diet (especially in paediatric epilepsy centres). Since the genetic causes of epilepsy are an increasing field of knowledge, genetic counselling should be available. Patients should be given the opportunity to participate in high quality clinical research where appropriate.

The treatment of difficult epilepsy patients in specialized centres is cost-effective, e.g., revised therapeutic schemes and epilepsy surgery render a substantial number of patients with drug-resistant epilepsy seizure free. This considerably reduces the direct and indirect costs for epilepsy patients. It is obvious that the academics working in these centres should be educated at experienced centres and undergo continuous quality monitoring and ongoing training.

Harmonization of treatment infrastructure and guidelines of epilepsy across Europe

There is still a considerable variance in the treatment gap between countries within Europe ([Brodie et, 1997](#), [Malmgren et al, 2003](#), [Eucare 2003](#)). In particular, the number of specialized centres per million, as outlined above, is not available in any one country. In addition, epilepsy surgery is at a high level in Austria, France, Italy, Germany, the Nordic countries, Spain and Switzerland. Other countries are developing well. A few eastern European countries, especially in rural areas, still show a large gap between what is there and what should be there ([Jedrzejczak et al, 2013](#)). In order to harmonize the treatment care of patients in Europe, the guidelines of the various countries should be summarized and a European guideline outlining standards of care should be developed, in keeping with the recent European Written Declaration on Epilepsy ([Baulac M et al, 2012](#)).

Epilepsy in the Developing Brain

Epilepsies are a major cause of neurological morbidity in children. The average annual rate of new cases of epilepsy is approximately 5-7 cases per 10,000 children from birth to age 15 years and, in any given year, about 5 of every 1,000 children will have

epilepsy. Seizures in preterm and newborn babies remain the most frequent neurological problem in neonatology intensive care units and it is currently unclear whether early seizures are the cause of long-term neurological deficits. Experimental studies on animal models indicate that epileptogenesis and cognitive deficits result from early seizures, but the underlying mechanisms are only partially understood ([Lombroso, 2007](#)).

Fundamental questions

Important advances have been made in determining the genetic basis of many forms of childhood epilepsy, developing appropriate transgenic mouse models, supportive computational models are emerging, and a European Regulation for Paediatric Drug Development is available. There are efficient research networks operating on this field and ready to develop innovative projects which involve interactions of clinicians, geneticists and neuroscientists. Convergence of concepts, data, networks, technological and regulatory improvements have emerged during the last decade. These developments have set the stage to ask fundamental questions that need to be addressed to make further progress:

- Why do certain seizures emerge or regress at particular ages and to what extent can final remission be predicted?
- How do developmental malformations, such as cortical dysplasias, lead to seizures and how can we target epileptogenic mechanisms?
- Why is there a latency delay from genetic mutation or appearance of a congenital dysplasia to seizures later in life? Is it possible to devise preventative strategies?
- When and how is a neuronal or neuronal-glia network transformed into an epileptogenic network?
- How might abnormal epileptogenic networks interfere with normal brain function?
- What are early structural or functional markers of epileptogenicity?
- Are there biomarkers of drug resistance and of cognitive dysfunction associated with the epileptic activity?
- Why do homeostatic mechanisms fail to prevent epileptogenesis?
- Which epigenetic factors contribute to epileptogenesis and epileptic seizures?
- Why phenotype diversity (mutation of the same gene yield different syndromes) or phenotype similarity (mutations on different, apparently unrelated, genes) give way to the same syndrome)

Short-term and medium-term research priorities: understanding the mechanisms of various childhood epilepsies

Factors that are known to increase the risk of epilepsy in children include malformations of cortical development, genetic alterations of developmental genes, certain inherited metabolic conditions, head trauma, CNS (central nervous system) infection/inflammation and hypoxia/ischemic conditions. However, these account for just 25% to 45% of cases and, thus the etiology of most cases of the epilepsies remains obscure (Cowan, 2002). Genetic studies have identified several of the genes associated with cortical malformations, which are often associated with pharmaco-resistant epilepsy (Guerrini et al., 2008). Extensive or multifocal malformations participate in complex epileptogenic networks, making neurosurgical treatment unfeasible. To make progress, we need:

- post-genomic research on malformations of developmental brain disorders and parallel studies on surgical tissue, allowing investigations from bench to bedside and back
- to consolidate and expand our knowledge on the causal heterogeneity of pediatric epilepsy
- to develop experimental models to elucidate the mechanisms of epileptogenesis in immature brain
- to expand our knowledge on the mechanisms underlying cognitive dysfunction in age-related epileptic encephalopathies
- to perform trials in age-related epileptic encephalopathies in small but homogeneous patient populations using innovative trial designs

Long-term research priorities: translating the mechanistic knowledge to treatments

Antiepileptic drugs (AEDs) that are used to treat seizures in infants, children and pregnant women may affect brain development and have long-term neurodevelopmental consequences. Voltage-dependent channels, neurotransmitter-operated receptors and transmitters constitute the molecular targets of AEDs, but the same targets also regulate developmental processes, such as cell proliferation, migration, differentiation and physiological apoptotic cell death (Kaindl et al., 2006; Marsh et al., 2006). As a consequence, cognitive deficits found in about 25% of epileptic children often result from a conjunction of different factors: the underlying etiology, the use of AEDs, and the epileptic activity (Berg et al. 2010).

New AEDs are usually designed for adulthood and using animal models of adult forms of epilepsy while it is clear that mal-developmental processes cause epileptogenesis and determine epilepsy features in children, including in some instances, drug resistance and the propensity to manifest as epileptic encephalopathies ([Ben-Ari and Holmes, 2006](#)). Therefore, childhood epilepsy is a specific problem that cannot be dealt with like a subset of adult epilepsies. Unfortunately, at present, clinical trials of novel AEDs in pediatrics are scarce, especially in the epileptic encephalopathies. Therefore, we need to:

- design innovative strategies to prevent and cure childhood epilepsy, and to prevent cognitive deterioration taking advantage of new genetic tools aimed at reducing the activity of specific neurons within a network and applicable to epileptogenic neuronal networks
- identify age- and disease-specific drug targets and translate these into drug discovery and novel trial designs

New targets for innovative diagnostics and treatment

Current AEDs aim at controlling the main clinical expression of epileptic disorders, the seizures. More than 15 new AEDs have become available in Europe since the early 1990s and they have improved the medical treatment of epilepsy by providing more treatment options, with a better tolerability and safety, fewer interactions with concomitant medications, and lower teratogenicity. However, none of the new AEDs has demonstrated superior efficacy over the prior generation AEDs, such as sodium valproate and carbamazepine ([Perucca, 2011](#)). This likely reflects the fact that all current AEDs target neurotransmitter release or receptors and ion channels involved in regulating neuronal excitability, but not mechanisms inherent to the pathophysiology of drug resistance and/or the disease.

This emphasizes the importance of identifying novel targets for future AED discovery and development that may permit to discover new AEDs with improved efficacy for drug resistant epilepsy or to enable to alter the course of the disease ([Galanopoulou et al., 2012](#)). Importantly, this also holds the potential to provide a positive business case, and thereby, to incentivize the pharmaceutical industry towards future AED discovery and development. Recent progress in the understanding of the mechanisms involved in

epileptogenesis, seizure emergence (ictogenesis), and drug-resistance holds promise for discovery of new targets for innovative diagnostics and medical treatments of epilepsy ([de Curtis and Gnatkovsky, 2009](#); [Pitkänen and Lukasiuk, 2011](#); [Potschka, 2012](#)). Genetic and pharmacological validation studies can verify their validity before translation of preclinical findings to clinical studies. Combined development of novel diagnostics, biomarkers and new treatments would permit to identify relevant patient populations and disease- and target-relevant biomarkers to enable early, clinical proof of concept studies. This comprehensive approach would permit to personalize new medicine and to predict the therapeutic potential by progression to comparative phase II trials before investment in costly, confirmative late stage phase III trials.

Non-neuronal modulation of epileptic activities: glial cells and inflammatory processes

Glial cells (astrocytes and microglia) undergo phenotypic and functional alterations in epilepsy and the emerging concept of gliotransmission and the role of astrocytes as signaling units in the so-called tripartite synapse support the crucial contribution of glial cells to changes in neuronal function ([Devinsky et al., 2013](#)). This is supported by new evidence from experimental models of epilepsy and different pharmaco-resistant forms of human epilepsy showing that glial cells release neuromodulatory molecules (e.g. glutamate, ATP, cytokines) and thereby constitute an important role in seizure generation, maladaptive plasticity and comorbidities ([Vezzani et al., 2012](#)). For that reason, glial cells offer the potential for identifying targets for innovative diagnostics and treatments for epilepsy, but open questions for glia cells role in seizure generation still remain and relate to:

- role of glia in seizure initiation vs spread vs termination
- functional/phenotypic changes in glia during ictogenesis and epileptogenesis by differentiating homeostatic from deleterious effects
- role of glia in pharmaco-resistance and blood-brain-barrier (BBB) dysfunction
- role of glia in comorbidities
- strategic therapeutic interventions targeting glia to modify their function to boost beneficial clinical outcomes

In addition, key questions remain in order to identify optimal pharmacological anti-inflammatory interventions:

- finding master regulators of the pathologic inflammatory cascade in epilepsy
- studying the time- and cell-specific expression of inflammation-linked targets during epileptogenesis in different models (symptomatic, genetic, adult, neonatal/childhood). Search for commonalities vs differences.
- understanding whether combined anti-inflammatory treatments may lead to improved clinical outcomes, as compared to individual interventions
- targeting resolution rather than prevention: how, when and where
- searching biomarkers of glia activation, brain inflammation, BBB opening for better patients stratification, diagnosis and prognosis

Non-coding genes as targets of the future in epilepsy

Based on data available, about 85% of the human genome is actively transcribed as non-coding RNA and non-coding RNA represents a major layer of regulatory control of gene expression that may be important in epilepsy ([Jimenez-Mateos and Henshall, 2013](#)). Research is beginning to uncover the complex functions of this diverse class of molecules, including control of epigenetics (the switches that turn genes “on” or “off”), and the process of gene expression, from transcription to translation.

MicroRNAs are an important class of small non-coding RNAs that have critical roles in brain development and function. Emerging research shows that levels of several microRNAs are altered by seizure activity in animal models, and are also different in regions of the brain from which seizures emanate in patients with epilepsy (e.g. the hippocampus)([Jimenez-Mateos and Henshall, 2013](#)). Targeting of several microRNAs in animal models has produced effects on seizure-damage and, in a single case, on evoked and spontaneous seizures. MicroRNAs are also present in body fluids, such as blood, and levels change in response to brain injuries, including seizures. Thus, microRNAs may also prove useful diagnostics and biomarkers of epileptogenesis. Open research questions to resolve include:

- improve understanding of non-coding RNA in regulating gene expression in epilepsy
- develop methods for targeting non-coding RNAs for therapeutic benefit
- focus on variants in non-coding RNA sequences in the human genome as risk factors for epilepsy
- identify microRNAs in biofluids that serve as molecular biomarkers of epileptogenesis

Toward a more accurate delimitation of the epileptic focus in a surgical perspective

Research on neurophysiological tools has significantly contributed to a better understanding and delineation of the epileptogenic zone in the patient's brain – and the human brain in general (Noachtar and Remi, 2009; De Ciantis and Lemieux, 2013). Based on scalp EEG and selected scalp voltage maps, the underlying electric source can be now estimated and visualized in the individual brain, with an excellent precision, both in children and adults, and then validated with operative success.

Co-registration of the EEG inside the scanner and functional MRI, allows localizing the epileptogenic focus more precisely. EEG-fMRI studies have also revealed large epileptogenic networks beyond the focus proper, i.e. there is not only a single diseased structure, but the whole brain is altered, or continues to alter if epilepsy is not controlled. The high temporal resolution (in the millisecond frame) of neurophysiological methods, such as the EEG, complements the other imaging techniques which have a much slower temporal resolution (at best several seconds only). Open research questions include:

- development of other biomarkers based on scalp EEG or intracranial EEG. A recent study on prolonged intracranial EEG suggested that patients' diaries are imperfect
- development of tools to better determine (non-invasively) the *extent* of the epileptogenic zone
- characterization of dysfunctional large brain networks: if they are known, other therapies aiming at neuromodulation via selected nodes or neuroprosthesis (memory, motor functions etc), could be envisaged
- development of more powerful scalp and intracranial electrodes to be used in humans
- studies on neurophysiological parameters from human and animal cortex to better compare clinical and experimental findings

Innovative multidisciplinary approaches and treatment strategies

Gene and cell therapy has recently gained considerable attention as innovative treatment strategies for epilepsy (Wykes et al., 2012; Walker et al., 2013). Gene therapy is often based on viral vectors that are replication deficient but that can transduce the genes of interest into the neurons of the brain, and thereby produce and release the protein that would have a therapeutic effect. Cell therapy is based on genetic manipulation of stem cells,

followed by their transplantation into the brain, thereby replenishing degenerated neurons and, at the same time, delivering the protein of interest into the epileptic tissue.

A specific potassium channel Kv1.1 and combinatorial approach of neuropeptide Y and its receptor Y2, are two recent examples that demonstrate anti-epileptic effect of one-time gene therapy treatment in various chronic models of epilepsy (Noe et al., 2012; Wykes et al., 2012). A combinatorial gene therapy approach with FGF-2 and BDNF, administered shortly after the epileptogenic insult, demonstrated that gene therapy can also exert anti-epileptogenic effect.

Optogenetics, the most sophisticated gene therapy approach, comprise two membrane proteins from one-cellular organisms, channelrhodopsin-2 and halorhodopsin, selectively expressed in specific populations of mammalian neurons. NpHR-based inhibition of excitatory neurons, or ChR2-based activation of interneurons, has been shown to suppress seizure activity in various in vitro and in vivo models of epilepsy (Kokaia et al., 2013). These data provide evidence that optogenetic closed-loop devices could be developed to stop seizures, once they are detected.

The novel sources of stem cells from patients own somatic cells, e.g. skin fibroblasts, so-called induced pluripotent stem (iPS) cells, can differentiate into GABAergic neurons, and can be used in the future for transplantation to inhibit seizures (Hunt et al., 2013). In support, GABAergic neuronal progenitors, grafted into the hippocampus, decrease the occurrence of chronic electrographic seizures. Open research questions include:

- Gene therapy: viral vectors can transduce genes of interest into the neurons of the brain and, thereby, produce and release proteins that would have a therapeutic effect
- Cell therapy: genetic manipulation of stem cells followed by their transplantation into the brain
- Optogenetics : a combination of techniques from optics and genetics to control the activity of selective neuronal populations in the brain

What is required for prevention and cure?

The term ***epileptogenesis*** refers to the development and extension of tissue capable of generating spontaneous seizures, including the development of an epileptic condition and progression after the condition is established (Pitkänen et al., 2013). A multitude of

different insults and diseases affecting the brain are known to cause epilepsy, that is, they have an epileptogenic potential. **Primary prevention** of epilepsy refers to the prevention of the occurrence of such epileptogenic insults, for example stroke, CNS-infections and traumatic brain injury (TBI). Although this aspect of prevention should not be neglected, it is unlikely that primary prevention will be successful and significantly reduce the incidence of epilepsy in the foreseeable future. Hence, there is an urgent need to develop interventions that prevent the development of epilepsy in patients at elevated risk for epilepsy after brain insult (**secondary prevention or antiepileptogenesis**). This “insult” could be either acquired (e.g., TBI, stroke) or a genetic factor. **Tertiary prevention** refers to prevention of epilepsy-related adverse outcomes including injuries, sudden unexpected death, and suicide in people with established epilepsy. Strategies for such tertiary prevention also are not well developed and are especially important for the large group of people with chronic pharmaco-resistant epilepsy. Development of new interventions aiming at **cure** is also of particular relevance for this group of patients with epilepsy.

Antiepileptic drugs do not prevent the development of epilepsy, nor do they alter the natural course of the disease. Also, there are no indications that epilepsy has been cured with available drugs (Pitkänen and Lukasiuk, 2011). Current pharmacological treatment is thus symptomatic, rather than preventive or curative. Cure can only be considered to have occurred in some specific circumstances, such as when the cause of seizures had been eliminated by successful epilepsy surgery or when a genetic defect of childhood epilepsy is no longer relevant later in life. Since many such patients will continue to be at a higher risk of seizure recurrence than the general population, it can even be questioned if these patients have been completely cured in the strict meaning of the word.

Laboratory experiments have revealed several potential mechanisms that can be targeted by advanced technologies to prevent epileptogenesis as well as to cure epilepsy (Pitkänen and Lukasiuk, 2011). However, many more targets likely remain undiscovered. Also, translation of preclinical findings from laboratory to clinic remains a major challenge, which relates to factors such as identification of the right target population to be tested, availability of biomarkers for patient stratification and prediction of treatment response, optimizing the preclinical and clinical study designs, and eliminating the regulatory obstacles.

Identifying patient populations suitable for trials of antiepileptogenic interventions

The risk of epilepsy after TBI, stroke or infection amounts to 3-50% and is highest in the first year of follow-up (Annegers et al., 1988; 1998; Burn et al., 1997). The risk is significantly greater in patients in whom the underlying epileptogenic condition is severe or has specific clinical characteristics (*e.g.*, occurrence of acute symptomatic seizures). Such high risk patients for epilepsy after brain insults such as TBI, stroke or encephalitis/meningitis can, to some extent, be defined based on clinical criteria. Consequently, patients at highest risk of unprovoked seizures and epilepsy may be suitable candidates for clinical trials for antiepileptogenesis. Based on power calculations, antiepileptogenesis trials can be performed with limited numbers of patients, provided that only those at highest risk are selected, making the trials less costly. Availability of biomarkers to identify the endophenotypes with the highest risk of epilepsy, for example after TBI or stroke, would be critical to stratify the study populations for clinical trials (Engel Jr et al., 2013).

Taken together, antiepileptogenesis trials are technically, ethically, and practically feasible, provided that the correct target population is identified, a drug with a documented antiepileptogenic mechanism is selected, the duration of treatment is appropriate, and the duration of follow-up is sufficient for a sizable number of events (that is, seizure recurrences) to be collected.

Understanding the mechanisms of epileptogenesis to design innovative treatments

Experimental proof-of-concept studies have revealed that about a dozen different treatments can reduce the development of epilepsy and/or its severity or development of co-morbidities after brain insults such as status epilepticus or TBI (Pitkänen and Lukasiuk, 2011). However, many of these experimental treatments are unlikely to proceed to clinic. The reasons vary from mechanisms of actions of treatments, which could relate a high risk of adverse events to application routes of the treatments, to lack of powered preclinical studies that would reproduce the proof-of-concept data. Moreover, little attention has been paid to age-specificity of mechanisms of epileptogenesis. However, as the mechanisms of epileptogenesis are multiple, it is likely that many treatable targets can be revealed and tested in clinically relevant animal models. Therefore, efforts should be targeted to:

- identify epileptogenic **mechanisms** for different epilepsy syndromes at different ages, including genes and genetic variability. This includes the application of state-of-

the art **bioinformatics** to analyze available ('omics') data, predict disease pathways and novel therapeutic targets

- design **tools for higher-throughput screening** of novel treatments, including the design of novel drug screening assays (e.g. chemoconvulsant or genetic zebrafish models of epilepsies)
- develop **technologies** for higher throughput and easier to use video-EEG monitoring and drug delivery in animal models
- develop age- and syndrome-relevant **models** for studying mechanisms of epileptogenesis and efficacy of treatments
- **provide resources for validation of novel targets** for both acquired and genetic epilepsies in clinically relevant animal models and in study designs with clinically applicable endpoint

Remove obstacles in translation of preclinical discoveries to clinic

Although preclinical efforts are likely to yield candidate treatments to interfere with epileptogenesis, several obstacles will need to be overcome for clinical translation. Among these are:

- Difficulty in recruiting patients into clinical trials where only a minority would be expected to develop epilepsy
- Engaging the pharmaceutical industry to invest in an area where benefits may take several years to be demonstrated

Opportunities to interfere with early stages of epileptogenesis are limited, and a cure is what most patients want. However, although surgical resection may cure epilepsy, it is only rarely possible - one reason being proximity to eloquent cortex. Gene therapy is one of the novel approaches most likely to make an impact, and several promising preclinical advances have been reported. The first gene therapy has already been licensed to treat a metabolic disease, and CNS diseases are especially attractive because neurons are post-mitotic, reducing theoretical risks of oncogenesis. Moving towards clinical translation will require optimization of viral vectors and identification of the most effective way to suppress seizures, without interfering with normal function. Among the options are to manipulate RNA interference or epigenetic mechanisms; to overexpress of native proteins; and to

exploit the temporal specificity of optogenetics. It will also be important to meet the cost of making viruses to GMP standards and to address the limitations of animal models of life-long disease states. A realistic early stage clinical trial design would be to target an epileptogenic brain region that could be resected in the event that the gene therapy failed.

Priorities to achieve prevention and cure of epilepsy – a proposal for a European roadmap for translational research

Several of the unmet needs in epilepsy can be explained by the fragmentary (often inaccurate) information available. Most reports refer to small and/or selected (non-representative) populations. Differing definitions have been used to identify risk factors, putative causes, and prognostic indicators. Diagnostic tests vary across studies. Studies on the prevention of epilepsy have been frequently performed with inadequate designs. For these reasons, large population studies using the same design could help defining the entire spectrum of preventable epileptogenic conditions, identifying patients at higher risk of seizures and epilepsy, and collecting sizable samples of cases for therapeutic trials. In addition, a strict collaboration between European countries is envisaged in order to study mechanisms and biomarkers underlying epileptogenesis using common protocols. To reduce the gap between the lab and clinic, preclinical and clinical studies should be aligned to maximize the benefits:

- to support target-driven discovery and development of antiepileptogenic drugs for prevention and cure of epilepsy
- to establish a preclinical European Consortium for Antiepileptogenesis studies
- to establish a clinical European Consortium for Antiepileptogenesis studies
- to perform comparative preclinical and clinical proof of concept studies of antiepileptogenic drugs for prevention of epilepsy
- to establish a European Biomarker Consortium for identification of different endophenotypes of patients at high risk for epilepsy and disease progression. A subproject includes the establishment of a European Epilepsy database
- to establish an Academia-Industry Partnership to develop innovative technologies for preclinical and clinical seizure detection and drug-delivery

- to explore the possibility of developing a European Epilepsy Surveillance System to monitor the epidemiology over time and thus effects of future preventive interventions

Table 2. Roadmap to reduce burden and stigma, improve access to care, and outline the research priorities of epilepsy in Europe.

Reducing stigma and burden of epilepsy

- need for awareness
- change perceptions
- increase knowledge
- legislation

Improving standards of epilepsy care

- access to specialist after the first seizure
- access to epilepsy specialist for difficult-to-treat patients
- access to medical centers specialized to epilepsy
- harmonization of treatment infrastructure and guidelines of epilepsy across Europe

Understanding and treating epilepsy in developing brain

- understand the mechanisms of a diversity of childhood epilepsies
- translate the mechanistic understanding to therapies

New targets for innovative diagnostics and treatment

- assessment of the potential of non-neuronal modulation of epileptic activities: glial cells and inflammatory processes
- assessment of the potential of non-coding genes as targets of the future in epilepsy
- more accurate delimitation of the epileptic focus in a surgical perspective
- multidisciplinary treatments: gene therapy, cell therapy, optogenetics

Prevention and cure of epilepsy

- understand the mechanisms of different types of epileptogenesis to design innovative treatments
- apply novel tools in treatment discovery and screening
- remove obstacles in translation of preclinical discoveries to clinic
- establish European-wide preclinical and clinical consortia for antiepileptogenesis and biomarker identification studies

Co-morbidities of Epilepsy with Focus on Ageing and Mental Health

- identify factors that lead to cognitive impairment or behavioral and psychiatric co-morbidities in patients with epilepsy

- perform studies in large cohorts of patients using detailed phenotyping that show disease development in relation to cognitive and behavioral comorbidity as a precursor, as well as a consequence, of seizure occurrence
 - find biomarkers (e.g., metabolic, functional, molecular) that allow early identification of patients at risk for the development of severe cognitive impairment
 - understand mechanisms that induce AED-related cognitive impairment
-

Co-morbidities of Epilepsy with Focus on Ageing and Mental Health

Behavioral comorbidities in epilepsy are frequent and they affect profoundly the patients' quality of life, and sometimes more so than the seizures *per se*. They often go underdiagnosed due to an overriding therapeutic focus on the primary symptom of epilepsy: seizures. However, some of the comorbidities can stem from the treatment of the seizures themselves. Further research on the origin of comorbidities, and their effective management, can impact positively on the patients' quality of life, as well as contribute to the cost effectiveness of providing overall care and services to this population.

Whereas previous research has mainly focused on chronic pharmaco-resistant epilepsies, it is now time to direct research resources and effort to the beginnings of the disease, in order to understand where the opportunities are to influence a positive course of neurodevelopment and maturation, successful social integration, inclusion, and healthy ageing for those afflicted with epilepsy.

Increasing recognition of co-morbidities

As a consequence of recent advances in genetics and neuroimaging, and their impact on the pathophysiology of the epilepsies, new classification schemes are now being proposed that place greater emphasis on etiology than on phenomenology of seizures. At the same time it is increasingly recognized that the total burden of epilepsy is more than having seizures. Chronic epilepsy is frequently associated with co-morbid cognitive and behavioral problems causing poor psychosocial and occupational outcomes in adult life. Depression and epilepsy, or treatment related adverse events, were found to have a higher predictive value for quality of life than the clinical patient characteristics (Luoni et al., 2011). As for cognition, problems in memory and executive functions are prevalent (Helmstaedter & Witt, 2012) whereas depression is the most frequent psychiatric comorbidity (Ettinger et

al., 2004). In children and early onset epilepsies, developmental hindrance is very common - major behavioral problems in children being autism as well as hyperactivity and attention deficit disorders (Taylor & Besag, 2013). As indicated by a representative population based study in England, associations of psychiatric and neuro-developmental conditions are overrepresented in epilepsy, and the association is stronger than in non-neurologic chronic diseases. The increased incidence of autism spectrum disorders in epilepsy, compared to other chronic disorders such as asthma, diabetes, and migraine, was interpreted as probably being an epilepsy specific comorbidity (Rai et al., 2012).

Biased focus on chronic epilepsies

During the past 30 years, clinical research has mainly concentrated on chronic epilepsy. A major hypothesis was that cognitive and behavioral problems accumulate with a longer duration of epilepsy leading to accelerated mental decline. Studies in chronic epilepsy patients, however, suggest that many cognitive problems may evolve at the beginning of epilepsy, if they are not present already before the first seizure, and that a large portion of the impairments seen in chronic epilepsy results from developmental hindrance. These studies indicate that early and successful interventions may protect against such negative cognitive development. Successful medical treatment can help to preserve cognitive capabilities and mental health but it may also cause additional problems (Ortinski & Meador, 2004). Whereas most side effects of antiepileptic drugs are dose or drug load related, some side effects, such as aggression and irritability with levetiracetam, or executive and language problems with topiramate, appear idiosyncratic and deserve genetic evaluations of individual susceptibilities to experience these side effects (Cirulli et al., 2012; Helmstaedter et al., 2013).

New onset epilepsies

Recent studies in large groups of untreated newly diagnosed and new onset epilepsies demonstrated that, dependent on the type of epilepsy, cognitive impairments are present in nearly half of the patients at the time of first diagnosis (Witt and Helmstaedter, 2012). Similarly, children with new onset epilepsies are often impaired from the beginning of the disease (Hermann et al., 2006) and there is evidence that academic and behavior problems in children antedate the first recognized seizure (Jones et al., 2007b). Like

cognitive impairment, psychiatric comorbidity is now considered not only a possible consequence but also a precursor of epilepsy. More likely it is the expression of a common underlying brain pathology ([Hesdorffer et al., 2006](#); [Jones et al., 2007a](#)).

Comorbidities as biomarkers for epilepsy outcome?

Psychiatric and cognitive problems in epilepsy patients can be considered to reflect the degree of brain damage or dysfunction and to be predictive for the epilepsy outcome. The idea is intriguing and there is indeed some evidence pointing in this direction ([de Araujo Filho et al., 2012](#)). There are, however, several studies showing, for example, no relation between depression and seizure control ([Adams et al., 2012](#)), which raises the question of whether different studies really refer to the same behavioral phenotypes ([Hoppe and Elger, 2011](#)). There is evidence that depression is related to morphological pathological changes underlying epilepsy ([Catena-Dell'Osso et al., 2013](#)).

The aged and ageing patient

A serious problem in epilepsy patients is the question of whether the co-morbidities of epilepsy may accelerate mental ageing and whether they pose risk factors for mental health at an advanced age. Whereas in children mal-development and retardation are likely, there is nevertheless greater plasticity which can help to restructure the cerebral functional organization ([Helmstaedter et al., 1997](#)). In older patients, processes of normal and even more pathological ageing may interact with the progress and treatment of epilepsy. Here the conditions match those in dementia, where brain damage in the history, as well as depression, represents risk factors for later mental decline ([Kessing, 2012](#); [Moretti et al., 2012](#)). At this point it must be mentioned that an epidemiological study from 2004 demonstrated a greater frequency of neurodegenerative conditions like Alzheimer or Parkinson disease in epilepsy patients, as compared to those without epilepsy ([Gaitatzis et al., 2004](#)).

What are the research priorities and what are short/medium/long-term objectives?

At present we have much information on the final outcome of epilepsy. Future research directions should include:

- identification of factors that lead to cognitive impairment or behavioral and psychiatric problems
- studies that show disease development in relation to cognitive and behavioral comorbidity, as a precursor as well as a consequence of seizure occurrence
- investigations of large cohorts of patients using multimodal and, whenever possible, longitudinal studies, coupled with detailed clinical phenotyping and appropriate omics.
- search of biomarkers (e.g. metabolic, functional, molecular) that allow early identification of patients at risk for the development of severe cognitive impairment.
- investigations into the mechanisms that induce AED-related cognitive impairment

Conclusions

ERF2013 was organized to prepare a roadmap to show how the Written Declaration on Epilepsy, approved by the European Parliament in 2011, can be implemented in practice, and what are the resources needed. A clear message was delivered to politicians and to policy makers that there is a need for further funding in epilepsy research within *Horizon 2020*. The top four research priority areas included (a) understanding epilepsy in the developing brain, (b) search of new targets for innovative diagnostics and treatments, (c) prevention and cure of epilepsy, (d) understanding epilepsy and co-morbidities with special focus on ageing and mental health.

Secondly, increasing awareness of epilepsy at every level of society is necessary to stress the importance of reducing the social burden, and the stigma associated with epilepsy, through targeted initiatives at EU as well as national and regional levels. In particular, the need for a European-wide epilepsy awareness campaign, supported by the European Commission, was stressed. The annual European Epilepsy Day, hosted on the second Monday in February for the past three years in the European Parliament, has been a major success and its continuation is to be encouraged.

Thirdly, there was a specific focus on the access to optimal standards of care, as well as a discussion surrounding the appropriate response to epilepsy care in Europe. There was general agreement of the need for specialised epilepsy centres to cater for 2-3 million inhabitants (4,000-6,000 patients). There was consensus that this course of action is highly desirable and requires support from politicians and decision makers in Member States and at EU level.

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