Review

Personalized translational epilepsy research — Novel approaches and future perspectives☆
Part I: Clinical and network analysis approaches

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ABSTRACT

Despite the availability of more than 15 new "antiepileptic drugs", the proportion of patients with pharmacoresistant epilepsy has remained constant at about 20–30%. Furthermore, no disease-modifying treatments shown to prevent the development of epilepsy following an initial precipitating brain injury or to reverse established epilepsy have been identified to date. This is likely in part due to the polyetiologic nature of epilepsy, which in turn requires personalized medicine approaches. Recent advances in imaging, pathology, genetics and epigenetics have led to new pathophysiological concepts and the identification of monogenic causes of epilepsy. In the context of these advances, the First International Symposium on Personalized Translational Epilepsy Research (1st ISymPTER) was held in Frankfurt on September 8, 2016, to discuss novel approaches and future perspectives for personalized translational research. These included new developments and ideas in a range of experimental and clinical areas such as deep phenotyping, quantitative brain imaging, EEG/MEG-based analysis of network dysfunction, tissue-based translational studies, innate immunity mechanisms, microRNA as treatment targets, functional characterization of genetic variants in human cell models and rodent organotypic slice cultures, personalized treatment approaches for monogenic epilepsies, blood–brain barrier dysfunction, therapeutic focal tissue modification, computational modeling for target and biomarker identification, and cost analysis in (monogenic) disease and its treatment. This report on the meeting proceedings is aimed at stimulating

much needed investments of time and resources in personalized translational epilepsy research. Part I includes the clinical phenotyping and diagnostic methods, EEG network-analysis, biomarkers, and personalized treatment approaches. In Part II, experimental and translational approaches will be discussed (Bauer et al., 2017) [1].

1. Introduction

Epilepsy affects over 50 million people worldwide and is thus one of the most common chronic neurological conditions. It is characterized not only by recurrent seizures but also by a 2- to 3-fold increase in mortality, stigma, psychobehavioral comorbidity, and decreased social participation and quality of life (QoL) [2]. Epilepsy is a heterogeneous group of conditions caused by many different underlying etiologies ranging from monogenic mutations to acquired focal lesions [3]. About one-third of patients have seizures that are refractory to current medical treatment, which is mainly directed at the suppression of epileptic seizures by globally decreasing neuronal excitability but not at comorbidities or the underlying neurobiology [4]. At the moment we are not able to prevent epileptogenesis (the development of epilepsy following an initial precipitating injury such as a febrile seizure or traumatic brain injury), and there are very few disease-modifying treatments [5].

Personalized medicine in epilepsy is currently restricted to patients with pharmacorefractory focal (mostly lesional) epilepsy syndromes who are candidates for epilepsy surgery [6]. The considerable progress in neuroimaging during the past decades and the increased utilization of invasive EEG, mainly stereo-EEG (s-EEG), allows the localization of the individual epileptogenic zone and its removal, destruction, or disconnection by microsurgery and stereotactic ablation in a small but growing number of patients, resulting in decreased mortality and increases in social participation and QoL [7,8]. Epilepsy surgery also provides access to viable epileptogenic tissue allowing unique insights in the neurobiology and pathophysiology of epilepsy, including the detection of epileptogenic somatic mutations [8–11].

Currently a second revolution in diagnosis is evolving rapidly — the detection of pathogenic gene variants in an increasing number of patients affected by epileptic seizures and encephalopathy starting during the first 2 years of life ("epileptic encephalopathies") [12,13]. The identification of causative genetic variants has given us insights into the molecular pathophysiology of epilepsy (and encephalopathies) and has facilitated the identification of molecular targets for personalized treatments in affected individuals that could potentially be used in larger patient groups. There are already examples of successful treatments directed at individual molecular mechanisms such as the use of the ketogenic diet in patients with mutations of glucose transporter genes, or the repurposing of approved drugs to treat, for instance, gain of function mutations in ion channels [13].

These recent developments open new avenues to personalized translational epilepsy research. In a broader context, translational medicine has been defined by the European Society for Translational Medicine (EUSTM) as an 'interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community' [14]. Major goals of translational research are given by the promotion of improvement in prevention, diagnosis, and therapies based on highly collaborative "bench-to-bedside" approaches [15,16].

Based on the "1st International Symposium on Personalized Translational Epilepsy Research" held in Frankfurt in September 2016 we explore here several approaches to personalized translational epilepsy research.

2. Comprehensive deep phenotyping as a prerequisite for personalized medicine

Personalized medicine is based on precise phenotyping that allows the identification of well-defined groups of patients that are amenable to specific treatment approaches. The recognition of relevant and treatable factors in these groups allows the development of tailored therapeutic approaches. Even with the advent of whole genome screening, the complexity of the interaction between genetic, environmental, and stochastic processes means that deep phenotyping still plays a critical role [17]. Such a comprehensive approach encompasses different levels of information ranging from clinical features up to tissue functions, metabolites, protein, and cell function pathways as well as regulatory processes including the role of mRNA [17]. As a consequence, all available evaluation methods including patient's history, clinical examination, neuropsychological tests, imaging techniques, laboratory data, as well as electrophysiological and functional tests are suitable tools during the phenotyping process. This approach is expensive and time- and resource-consuming, and data processing and interpretation are challenging. Additionally, time and developmental dependence of the underlying pathophysiological conditions during the process of epileptogenesis are notable pitfalls in this process. As deep phenotyping comprises a huge amount of data, sufficient integration of different datasets is important [18]. A database like the Human Phenotype Ontology project (HPO) combined standardized descriptions of data with a branch tree for ranking the obtained information [18,19]. In both studies, this allowed the linking of apparently different conditions by similar features and the identification of new correlations between the underlying genetic condition and the phenotypic features. The "cross-disorder" relevance of several symptoms can thereby be established, and top-down as well as bottom-up approaches can be realized. However, this promising advance represents only a first step as the included epilepsy terms in this database are insufficient to provide a phenotypic description on the level required for deep phenotyping. The more detailed characterization of each level of information and its standardization will help to develop further computational disease models of epilepsy and extensive analysis of these data.

3. Quantitative MRI techniques to define epileptogenic lesions

Malformations of cortical development (MCD), including focal cortical dysplasia (FCD), periventricular nodular heterotopia, and polymicrogyria are common causes of refractory epilepsy, and their detection is crucial for successful epilepsy surgery [3]. FCD is often characterized by hypo-, de-, or dysmyelination in the subcortical white matter, changes that cause blurring of the gray-white matter junction and mimic increased cortical thickness in T2- and T1-weighted magnetic resonance (MR) images. These changes are often subtle and hard to identify by visual evaluation of data acquired with conventional MR sequences. It is particularly difficult to define the margin between normal and pathological brain with current techniques. Furthermore, cortex overlying and adjacent to nodular periventricular heterotopia has been shown to be epileptogenic but usually looks normal on conventional MRI [20]. One promising novel approach to improve the detection and delineation of pathological tissue in patients with MCD is the acquisition of quantitative MRI (qMRI) maps in patients with MCD, optimizing contrast characteristics for instance of the gray-white matter junction.

In contrast to conventional MR techniques which are based on the acquisition of data with different contrast weighting, the goal of qMRI is the mapping of specific tissue parameters, such as the relaxation times (T1, T2, T2*) and the proton density (PD). The advantage is that these maps provide exclusive information about the respective

parameter of interest and are not biased by any other parameter. This allows for the detection of microstructural pathologies that might go unnoticed in conventional MR images. Furthermore, as the parameter maps provide "pure" contrasts, they can be used to create synthetic MR data with improved contrast characteristics. The BIC in Frankfurt/Main provides a series of qMRI techniques that have been applied in several previous studies, such as the investigation of patients with multiple sclerosis [21], glioblastoma [22], Parkinson's disease [23], and stroke [24].

4. Assessing network dysfunction in epilepsy

Network dysfunction in epilepsy has recently received a lot of attention because neuroscience, in general, has moved from focal to more dynamic approaches that reveal temporal patterns in distributed neural representations; such spatially and temporally distributed networks are also likely to contribute to the development of epileptic seizures. One of the major challenges in defining functional anomalies in epilepsy is the heterogeneity of disease manifestations.

The changes that occur in neural networks have been investigated by numerous functional imaging experiments that have compared interictal resting-state networks in patients with epilepsy with ones observed in healthy controls using fMRI. Both hyper- and hypoconnected brain networks have been documented, suggesting either prominent patient heterogeneity or the fact that the BOLD response may blur temporal dynamics that are necessary for detection of epilepsy-related changes.

Interictal combined EEG/MEG recordings represent a promising experimental approach that offers optimal temporal and spatial resolution. Using this methodology, Englot and colleagues documented that the putative epileptogenic zone has increased imaginary coherence with the rest of the brain [25] and that this measure correlated well with seizure freedom upon resection of this area.

While this measure is still relatively coarse and the physiological meaning of global connectivity remains obscure, a more refined analysis of epileptogenic networks can be performed on ictal data. Using intracranial EEG from invasive recordings, Bartolomei and colleagues proposed an epileptogenicity index that takes the onset of high frequency oscillations in the acquired data into account [26]. While the number of areas with higher epileptogenicity index increases with the duration of epilepsy, the clinical relevance of this measure for surgery outcome has not yet been confirmed [27].

Disappointingly, other research on epileptic networks using graph theoretical descriptors of interictal functional networks [28,29] or functional connectivity measures based on direct electrical stimulation [10] has not yet been shown to predict surgical outcome.

A novel approach will be the study of information theoretic measures in focal epilepsy. Invasive and noninvasive recordings of patients with focal, particularly temporal lobe, epilepsy can be used to investigate the effects of antiepileptic drugs on these measures. Furthermore, based on these measures, the relationship between information theoretic measures in neural recordings with the individual phenomenology can be studied. The rationale behind this approach is the assumption that information processing will be reduced in epileptic networks and that the identification of reliable measures could help in defining the individual epileptogenic zone and explain neuropsychological findings. Such an approach of personalized diagnostics differs substantially from previous group analyses.

5. Large-scale networks underlying cognitive functions revealed by s-EEG in patients with epilepsy

The field of cognitive neuroscience concerns itself with how cognitive abilities arise from brain activity. Language and music are just two examples of cognitive systems that have been and continue to be the subject of considerable research. However, they demonstrate clearly the highly distributed nature of information processing in the brain. Specifically, functional imaging methods have revealed that both language and music processing involve not just auditory cortices but also several medial temporal as well as frontal regions [30–32]. With regard to possible mechanisms underlying the transfer of information within such distributed brain networks, oscillations are considered a highly likely candidate [33].

Magnetoencephalography, by offering a window into neural oscillatory activity, has allowed the temporal dynamics of information transfer within the brain to be explored. However, stereotactic EEG recordings, in particular, give access to neural data at a combined spatial and temporal resolution that is not offered by noninvasive methods. As a result, a growing research effort has taken advantage of s-EEG data to explore the neural substrates and mechanisms underlying different aspects of human cognition and affect. In our work, for instance, we have used s-EEG to show that oscillatory interactions (specifically in the theta and alpha band) between the auditory cortex, the amygdala, and the orbitofrontal cortex are modulated during music listening. Using a directed measure of connectivity (Granger causality) allowed us to further demonstrate that the strength of directed flow from the amygdala to the orbitofrontal cortex, specifically, is highly predictive of the valence of the sound heard [34].

Critically, studies such as ours may not only offer insights into how information processing is distributed across large-scale brain networks but may also offer a deeper understanding of how epilepsy networks are organized for use in clinical applications. Novel methods that detect information coded in time (defined as information-carrying modulations of neural oscillations, [35]) provide additional insights compared to those focusing on spatially distributed information. An ever growing interest in revealing such neural temporal dynamics has led to a proliferation of several different methods for inferring functional connectivity [36]. While the use of these numerous methods has led to considerable insights regarding the distributed nature of information processing, one particular method, transfer entropy, seems to offer several additional advantages. First, being model free, it reduces the need for potentially inaccurate model assumptions. Secondly, it has the power to reveal both linear and nonlinear interactions allowing detailed analysis of directed interactions at different descriptive levels [37].

The use of methods like transfer entropy to provide in-depth knowledge of information transfer during different cognitive tasks offers the possibility to identify affected cognitive networks in individual patients. The tendency has been for clinicians to base their decision-making on descriptive analysis of brain activity; advanced network and information theoretic measures will improve the precision of the description of ictal networks for highly personalized therapeutic treatment.

6. The ketogenic diet as a treatment concept for epilepsy and underlying tumors

The ketogenic diet has been investigated as treatment for epilepsy since the 1920s but only more recently have the first randomized clinical trials been reported [38]. For some rare syndromes, like GLUT1 deficiency syndrome, the primary mechanism of action of the ketogenic diet apparently consists in providing the brain with alternative energy sources. For most cases of intractable epilepsies, however, the anticonvulsant mechanisms are only partially understood and probably involve diverse mechanisms. Both the ketogenic diet as well as cyclic fasting lead to increasing levels of ketone bodies (3-hydroxybutyrate, acetoacetate) in the serum that can readily be used for energy production by cells with the appropriate enzymatic machinery, i.e., neurons. Due to glucose addiction of cancer cells, dietary interventions have also drawn great interest as a potential cancer treatment and promising in vitro data have been reported both of combinations with radio- and chemotherapy [39]. Currently, clinical trials to investigate cyclic fasting and ketogenic diets in brain tumors are underway (e.g., NCT01754350) [40]. How different dietary interventions affect metabolism of tumors or

brain tissue in humans in vivo has not been closely monitored thus far and would be essential for a more in depth understanding of dietary interventions as a treatment concept for epilepsies and brain tumors. Microdialysis offers the opportunity of a dynamic measurement of metabolites in tissue. We aim to include patients with a suspected glioma and an indication for a brain biopsy in a study (ERGO 3) where a microdialysis catheter is placed in the biopsy canal. After a period of dietary interventions, the lesion is resected and the catheter is removed while the patient is still fasting. This will allow important insight into the metabolism of glioma and brain tissue during dietary interventions as well as a correlation of metabolic changes with MRI and histology data.

7. Personalized treatment approaches for monogenic epilepsies

Currently available antiepileptic drugs (AED) reduce the likelihood of seizure occurrence but do not modify the underlying disease process. The genetic causes of a number of monogenic epilepsies have been discovered recently. Understanding the pathophysiological consequences of the identified mutations increasingly allows the initiation of therapies that modify the effect caused by the specific mutation (precision medicine). This approach often includes repurposing of already available drugs that are approved for the treatment of different diseases [13].

Current state of the art: The following precision medicine treatments are established and in routine clinical use: The classic ketogenic diet in GLUT1 deficiency syndrome bypasses the defective glucose transport across the blood–brain barrier. The modified Atkins diet, a less strict dietary regimen, has also been shown to be effective [41]. The mTOR inhibitor everolimus inhibits the overactive mTOR pathway in tuberous sclerosis [5]. Sodium channel blockers have been observed in clinical settings to be particularly effective in epileptic encephalopathy (EE) due to KCNQ2 and potentially SCN8A and SCN2A mutations. Sodium-channel blockers can lead to worsening of SCN1A-positive Dravet syndrome. The AED stiripentol has been particularly effective in Dravet syndrome.

Other treatments have been reported based on hypothetical considerations and have shown efficacy in a few case reports. These include the potassium channel opener retigabine in EE due to KCNQ2 loss-of-function mutations and the potassium channel blocker quinidine in EE due to KCNT1 gain-of-function mutations. Fenfluramine, which was developed as an appetite suppressant but withdrawn from the market due to serious adverse events, has shown outstanding efficacy in smaller case series of Dravet syndrome.

Additional treatments are suggestive based on hypothetical considerations and/or efficacy in animal models but no or only single reports in patients are available. This includes the off-label use of the mTOR inhibitor everolimus in patients with familial focal epilepsy with variable foci due to mutations in the GATOR1 complex (DEPDC5, NPRL2, NPRL3) leading to mTOR disinhibition, the NMDA receptor antagonist memantine in genetic focal epilepsies of childhood due to GRIN2A/2B mutations and the potassium-channel blocker 4-aminopyridine in patients with EE due to KCNA2 gain-of-function mutations.

Future perspective: Large international efforts catalyzed by the ongoing progress in epilepsy genetics will produce extended cohorts of patients with similar mutations that will considerably advance the development of new precision medicine treatments.

8. Assessment of cost-efficacy of personalized therapy

Taking into account the high prevalence, the chronic course, associated utilization of healthcare resources and loss of productivity, epilepsy imposes a substantial burden on individuals, their caregivers, and society as a whole [42]. Given the limited healthcare resources, it has become essential to gather reliable cost estimates as a scientific basis for resource allocation and health policy decision making. This remains particularly important as the introduction of newer antiepileptic drugs, the use of generic medication, the marketing of brain stimulation devices,

epilepsy surgery, and the breakthrough of newer treatment options may cause a shift in the distribution of cost components resulting in an increase or decrease of total costs. However, costs should not be considered out of context but must be related to treatment success and increase in QoL. Therefore, close monitoring and prediction of the economic consequences of the introduction of new therapies into the market remains pivotal. These economic evaluations are particularly important in patients with intractable epilepsies as these are associated with high costs [43,44] While there is large evidence linking intractable epilepsies to a high resource allocation, there is very little known about health economic consequences of more severe epilepsies, for example, associated with epileptic encephalopathies or specific syndromes such as TSC or Dravet syndrome (DS). A pilot study in DS demonstrated the high resource consumption driven by hospital treatment and emergency admissions in this severe childhood epilepsy [45]. The influence of an adjunctive therapy with stiripentol and clobazam on costs in refractory DS showed an increase in medication costs that was offset by reduction in hospitalization and emergency admissions [45]. Unfortunately, this study did not evaluate indirect costs in terms of loss in the professional work of the parents due to the epileptic seizures or the quality of life in patients and caregivers, both important factors associated with wellbeing. Analysis of single patients showed that a decrease in costs and decrease in seizure frequency were not always correlated. This clearly demonstrated that treatment success does not depend upon a single outcome parameter such as seizure frequency. The overall impact of a new therapy on seizure frequency, seizure severity, cognitive improvement or side effects, and quality of life in patients and their caregivers has to be taken into account. Further studies are warranted to provide comprehensive data on the course of disease in epileptic encephalopathies or specific syndromes such as TSC or Dravet syndrome.

9. Biomarkers of epilepsy and epileptogenesis

Epilepsy is characterized by paroxysmal changes in neural dynamics, giving rise to short-lived interictal discharges and epileptic seizures. As epileptic neural events propagate across specific but possibly variable networks, the involved networks change their long-term activity due to neural plasticity. These structural and functional changes offer the opportunity to develop biomarkers aimed at detecting specific features of epilepsy and epileptogenesis [46]. A good biomarker should optimize the trade-off between the following requirements: sensitivity, specificity, predictive value, robustness, and accessibility. While sensitivity and specificity are inherently competing concepts that influence the predictive value of a given biomarker, robustness and accessibility are determined by neurobiological and technological factors. In the context of clinical epileptology, EEG and MRI are currently the most widely used techniques, while other methods including molecular biomarkers measured in blood and cerebrospinal fluid (CSF) are increasingly evaluated. Electroencephalography biomarkers in daily routine involve the localization of interictal epileptiform discharges and seizure detection. On the other hand, automated approaches powered by recent advances in (un-)supervised feature extraction and machine learning help to improve robustness and provide a means of reproducibly processing large data sets [47]. Moreover, they offer the chance to yield biomarkers not easily detected by the human observer. Important examples are EEG-derived functional connectivity measures and the quantification of pathological high-frequency oscillations associated with the epileptogenic zone. In particular, these methods can be used to characterize alterations of interictal brain function (see above). Structural MRI is related to the pathology underlying epilepsies and serves to localize and delineate epileptogenic lesions. With respect to imaging techniques, functional MRI approaches provide insight into metabolic changes and the activity of subcortical brain regions not accessible to EEG. The simultaneous recording of surface EEG and functional MRI has deepened our understanding of spike-related epileptic networks beyond basic spike localization [48]. Furthermore, given the wide

variety of experimental designs available, functional connectivity during the interictal resting state and task-specific activations provide a multidimensional view on brain function in epilepsy and may help to bridge the gap with neuropsychological and behavioral biomarkers of epilepsy. One example of novel molecular biomarkers derived for body fluids are expression profiles of microRNA (miRNA) in plasma and CSF which are differentially regulated in epilepsy and also, importantly, in response to an epileptogenic insult (Raoof et al., unpublished data). MicroRNA has the advantage that it can be directly involved in the regulation of multiple pathways relevant to the neurobiology of epilepsy [49]. If such biomarkers are sensitive, specific, and have high positive predictive value, they may serve to detect subpopulations at high risk for developing epilepsy for inclusion in trials investigating antiepileptogenic interventions, for example, in patients following head trauma or prolonged febrile seizures. In summary, designing biomarkers of epilepsy and epileptogenesis remains a challenging but promising goal in terms of information integration and translational clinical epileptology.

Conflict of interest

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